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**ABSTRACT**

*Background:* Percutaneous Cervical Cordotomy (PCC) offers pain relief to patients with unilateral treatment-refractory cancer related pain. There is insufficient evidence about any effects of this intervention on patients’ quality of life.

*Method:* Comprehensive multimodal assessment to determine how PCC affects pain, analgesic intake and quality of life of patients with medically refractory, unilateral cancer related pain.*Set in a* Multidisciplinary, tertiary cancer pain service. Patient outcomes immediately following percutaneous cervical cordotomy were prospectively recorded. Patients were also followed up at 4 weeks.

*Results::*Outcome variables collected included: background and breakthrough pain numerical rating scores before PCC, at discharge and 4 weeks post procedure; oral morphine equivalent opioid dose changes, Patient’s Global Impression of Change, Eastern Cooperative oncology group (ECOG) performance status and health related quality of life score i.e. EQ-5D-5L.

*Conclusions****:*** Despite significant improvement in pain and other standard outcomes sustained at four weeks, there was little evidence of improvement in EQ-5D scores. In patients with terminal cancer, improved pain levels following cordotomy for cancer-related pain does not appear to translate into improvements in overall quality of life as assessed with the generic EQ-5D measure.

**BACKGROUND AND INTRODUCTION**

Percutaneous cervical cordotomy (PCC) was introduced by Mullan in 1963[[1]](#endnote-2)to treat chronic pain; however, the PCC indication was later narrowed to intractable malignancy-related pain due to concerns about persistent procedure-related morbidity. PCC is now recommended only for those with a limited life expectancy[[2]](#endnote-3) of less than 12-18 months. PCC is deemed less invasive than open surgical cordotomy, which is also associated with higher morbidity[[3]](#endnote-4),[[4]](#endnote-5). PCC interrupts the spinothalamic tract in the anterolateral quadrant of the spinal cord at the level of C1/C2 by radiofrequency ablation; it thus causes *contralateral* loss of pain, itch and temperature perception below the level of the lesion[[5]](#endnote-6),[[6]](#endnote-7). Nociceptive pain is thought to respond better to cordotomy than neuropathic pain[[7]](#endnote-8).

Mirror pain (opposite the side of initial pain in a mirror image area of the body) can occur in up to 20% of cases post PCC, and respiratory failure can be fatal. Thus, there is a need for careful patient selection and counselling including assessment of respiratory reserve. Patients who have a life expectancy of less than 12-18 months and who have cancer-related focal, unilateral pain below the shoulder can be successfully rendered pain free. Few studies have looked at the impact of percutaneous cervical cordotomy (PCC) on patient’s quality of life, and we have therefore assessed this prospectively.

Cancer related pain is common and is present in up to 70% of patients as their disease progresses[[8]](#endnote-9),[[9]](#endnote-10). It is one of the most feared symptoms of having end-stage cancer[[10]](#endnote-11) and severely impacts quality of life. Cancer pain depends on the disease site and it can be unilateral or bilateral.

The WHO ladder is a three-step approach for the treatment of cancer-related pain, which advocates escalating doses of opioid therapy. For 10-15% of patient’s cancer-related pain remains uncontrolled even with the use of strong opioids (WHO step 3)[[11]](#endnote-12) and additional patients report significant opioid-related side effects[[12]](#endnote-13).

Cordotomy is likely to offer near complete pain relief in over 80% of suitable patients[[13]](#endnote-14).Such profound pain relief should improve quality of life and survival post PCC as noted with intrathecal pumps for cancer related pain[[14]](#endnote-15); however other factors related to having cancer may independently impact on patients’ quality of life such as loss of energy, physical endurance and spread of cancer to vital organs.

**METHODS**

**Patient selection**

This project was approved by the Walton Centre NHS Foundation Trust for service evaluation and anonymised data is submitted to national UK cordotomy registry.

Patients who were selected for PCC had been referred by Oncology, Pain or Palliative Medicine services from our region and nationally. These patients underwent multidisciplinary assessment in our Pain and Palliative Medicine joint regional clinic. Patients were thoroughly counselled about the risks and benefits of PCC, and the need for them to be awake and co-operative with the operator at the time of procedure though they may be lightly sedated. The process of fully informed consent also included provision of written information to the patient and family, sharing our audited outcomes for PCC13 and repeat discussion on risks and benefits as required.Where assessments were difficult because the patient was distressed due to overwhelming ‘total pain,’assessments were repeated over further appointments. We engaged family members in the discussions and talked about how procedure-related anxiety could be managed.The selection criteria for PCC at our institution comprises of the following:

1. Malignant disease with *uncontrolled, unilateral pain* below fourth cervical dermatome (the collar bone) and a life expectancy of less than 12-18 months.
2. Increasing requirement for opioids and adjuvant analgesics with inadequate control of pain or disabling drug-related side effects.
3. Able to lie supine for at least 45 minutes.
4. Patient understands the risks and is able to tolerate the procedure.
5. Sufficient respiratory reserve

To further clarify the first criterion ‘*uncontrolled pain’*we provide an example of one of the typical cases in our case series. “A 58 years female with history of right renal cancer with sacral plexus invasion with severe right leg pain worse on weight bearing. She had received palliative radiotherapy, chemotherapy including immunotherapy. She was on oxycodone slow release 360 mg BD, oxycodone immediate release 50 mg QDS, pregabalin 300mg BD, naproxen 500mg BD and had undergone an unsuccessful trial of oral steroids”.

**PCC Technique**

PCC is performed with fluoroscopic guidance. The patient is positioned supine in the operating theatre, with the head supported and restrained in a Carbon fibre Cordotomy headrest (Wolverson X ray limited UK) and oxygen is administered by nasal cannula. Intravenous access and monitoring including pulse oximetry, ECG, NIBP is established and sedation is administered as required. The aim of sedation is to maintain verbal contact with the patient so that they are comfortable and able to communicate with the operator. The skin spinal needle entry point is located over the C1/2 intervertebral foramen, contralateral to the site of pain, and is approached fluoroscopically under local anaesthesia (20G Quincke tip).A myelogram is performed using Lipiodol®; a lipid-based contrast agent. Myelogram demonstrates the position of the spinal needle in relation to the dentate ligament. The Neurotherm® NT1000 Radiofrequency generator is used in this cordotomy setting for its audible impedance tone. Cordotomy electrode with 2 mm active tip is introduced through 20G spinal needle into the anterolateral quadrant of the spinal cord to ascertain sensory stimulation at 50 Hz (hot or cold sensation) to the contralateral side of the body i.e. where the pain is.2Hz (motor) stimulation is used to confirm that the cordotomy electrode placement is not close to or within the ipsilateral corticospinal tract. Once the target area is localised, incremental radiofrequency heat lesions are made starting from 75 degrees Celsius to 85 degrees Celsius up to desired reduction/abolition in spinothalamic sensations. Each lesion is done for 25 seconds.

In the post-operative period, the patients have standard observations and usually remain as an inpatient for 3-5 days. Post procedure, opioids are usually prescribed at a 50% dose reduction and titrated according to patient response.

**Data collection**

Data relating to baseline status, technical procedure and post-procedure outcomes (including 4 weeks follow up) was collected prospectively from May 2016 to March 2018 in all 25patients treated during this period by a Consultant in Pain Medicine (MG).

Data included patient demographics, pain description, breakthrough and background numerical pain scores before PCC, and patients’ quality of life i.e.EQ-5D data including the visual analogue scale of general health. Data regarding anxiety and depression for the EQ-5D was collected for only the last nine patients and is therefore not included in this analysis. Eastern Cooperative Oncology Group (ECOG) scores on performance status, PGIC (patient’s global impression of change), sleep quality, and analgesic dose change data were also collected.

Procedural technical data included the quality of the myelogram, the type of sensation and motor parameters observed on sensory (50 Hz) and motor stimulation (2 Hz,) and the number of radiofrequency lesions.

On discharge any adverse effects such as mirror pain, dysaesthesia, limb weakness, headache, neck pain or any other complications were actively recorded. Follow up data collection at 4 weeks, either face to face or via telephone interview with the patient or carer reflected the pre-operative items regarding pain, quality of life, sleep and adverse effects; new pain sites(if any)were recorded.

Data was collected and recorded on spreadsheet using Microsoft excel before analysis and presented in graphs.

**RESULTS**

**Demographics**

25 patients underwent PCC over the specified period. The average wait from the time of assessment by the multidisciplinary team until PCC was performed, was 11 days (minimum 4 days, median 5 days). The mean length of stay post procedure was 2.72 days.

All patients had baseline data collected. The male/female ratio was about 2:1. The average age was 64.72 years (range 46-78, Table 1). Eight of the 25 patients were lost to follow up due to death (n=5) or inability to contact them (n=3); though we did have the outcome data for all patients at the point of discharge post PCC (Table 1).

|  |  |  |
| --- | --- | --- |
| **Demographic data** | **Pre-PCC Pain** | **Post PCC Pain and PGIC** |
|
| **Age****years** | **Gender** | **Diagnosis** | **Pain Site** | **Breakthrough Pain Score (0-10)** | **Background Pain Score (0-10)** | **Pain relief (%)** | **PGIC** |
| 63 | Male | Mesothelioma | Left chest | 8 | 2 | 90% | Very much better |
| 55 | Female | Cervical cancer | Right leg | 8 | 5 | 100% | Very much better |
| 62 | Female | Lung cancer | Left chest | 10 | 8 | 100% | Very much better |
| 50 | Female | Cervical Cancer | Left Leg | 5 | 4 | 100% | Very much better |
| 54 | Female | Lung cancer | Left Arm | 10 | 5 | 100% | Very much better |
| 71 | Male | Mesothelioma | Right chest | 10 | 7 | 100% | Much better |
| 66 | Male | Mesothelioma | Right chest | 8 | 10 | 100% | Much better |
| 69 | Female | Liposarcoma shoulder with brachial plexus invasion | Right Arm | 10 | 7 | 100% | Very much better |
| 58 | Female | Lung cancer | Right Arm | 8 | 5 | 100% | Very much better |
| 69 | Male | Lung cancer | Right chest | 10 | 8 | 100% | Much better |
| 69 | Male | Adenocarcinoma Rectum (metastatic) | Right chest  | 10 | 4 | 100% | Much better |
| 76 | Male | Mesothelioma | Right chest | 10 | 7 | 50% | Much better |
| 64 | Male | Mesothelioma | Right chest | 10 | 8 | 100% | Much better |
| 70 | Male | Mesothelioma | Right chest | 10 | 7 | 100% | Very much better |
| 73 | Male | Mesothelioma | Right chest | 10 | 7 | 100% | Slightly better |
| 55 | Male | Mesothelioma | Right chest | 9 | 6 | 100% | Much better |
| 75 | Male | Mesothelioma | Right chest | 10 | 8 | 100% | Much better |
| 58 | Female | Rectal cancer with sacral plexus invasion | Right Leg | 10 | 5 | 100% | Much better |
| 69 | Male | Prostate cancer with sacral plexus invasion | Right Leg | 10 | 8 | 100% | Much better |
| 55 | Male | Lung cancer | Right chest | 10 | 8 | 100% | Much better |
| 66 | Male | Mesothelioma | Right chest | 9 | 6 | 100% | Much better |
| 79 | Male | Metastatic Rectal Cancer | Right chest | 9 | 8 | 100% | Slightly better |
| 73 | Male | Lung cancer | Right chest | 9 | 7 | 100% | Slightly better |
| 75 | Male | Mesothelioma | Left chest | 10 | 8 | 100% | Slightly better |
| 70 | Female | Breast Cancer with axillary metastasis to brachial plexus | Right Arm | 10 | 10 | 100% | Much better |

Table 1: Baseline demographic data and post PCC outcomes at time of discharge

**Pain Scores**

Breakthrough and background pain scores pre-procedure, at discharge post procedure and at 4 weeks are shown in Figure 1. The median of the percentage change in breakthrough pain score was 100%. Similar effect sizes were seen relating to background pain both at discharge, and at four weeks. The average percentage reduction in breakthrough pain and background pain at discharge was 98% and 98.9%. At 4 weeks follow up it was 83.1% and 86.4% respectively (Figure 1). There were no patients in our cohort who did not report significant relief of the pain for which PCC was offered. There is data for 16 patients at four weeks due to loss of 9 patients to follow up (5 died and 3 could not be contacted and 1 did not provide a pain score).

**Impact on analgesics consumption and side effects**

None of the patients reported an increase in analgesic use.20 of the 25 patients (80%) were able to reduce oral morphine equivalent dose by more than 40% at discharge (Figure2). The mean oral morphine equivalent dose pre PCC was 489mg/24 hours (range 20mg-3280mg, median 280mg). One patient needed a urinary catheter for a few days post PCC; one patient suffered sinus tachycardia; one patient reported temporary weakness of the left lower limb; one had low oxygen saturations and opioid toxicity for a couple of days, and another had temporary opioid withdrawal. These side effects settled before their discharge. One patient reported mirror pain at the time of discharge.

**Impact of PCC on quality of life measures**

We were unable to convert our EQ-5D-5Lsub-category data for anxiety and depression due to missing data (see methods section). The EQ-5D-5L sub-category data at 4 weeks in comparison with baseline are presented in figure 3. Unexpectedlyapart from a significant change in the pain score, there were no changes in the other three assessed sub-categories. The EQ-5D-5L VAS score (0=’worst health you can imagine’, 100=’best health you can imagine’) was available for 17 patients at both baseline and 4 weeks. In these patients it changed from an average of 23 to 21.

**Patient’s global impression of change post PCC**

52% of patients reported being ‘much better’ at discharge on the patients’ global impression of change scale; 32% were very much better and 16% slightly better (figure 4). Majority of patients were pleased that they underwent PCC and will recommend to others in a similar situation. Some of the feedback at 4 weeks included: “pleased with the care provided”, “family relieved that patient passed away comfortably without pain at home”.

**ECOG results (performance status) at 4 weeks post PCC and sleep**

We did not observe any clear trend in this domain post PCC. Patients reported mild to moderate problems with their sleep at baseline, and this did not change at 4 weeks (n=17, not shown).

**DISCUSSION**

Our findings in this prospective audit of 25 patients treated with percutaneous cordotomy for intractable unilateral cancer pain support PCC as an effective and safe treatment, though requiring a period of hospitalisation (mean length of stay 2.72 days) for recovery and down-titration of analgesia post procedure. Opioid and adjuvant analgesics requirements following PCC were significantly reduced. At discharge most patients reported profound pain relief and considered themselves much/very much improved, but at 4-weeks follow-up quality of life scores for mobility, self-care, usual activities, and the overall EQ-5D VAS score remained unchanged vs. baseline, despite persistent analgesia.

As the incidence of cancer is rising (350,000 people in the UK diagnosed each year), the death rate is expected to rise from 160,000 per year to 193,000 per year by 2030[[15]](#endnote-16). The number of those affected by intractable cancer pain is expected to rise as the cancer incidence is rising and more people are living longer following cancer treatment. 45-56% of patients with advanced incurable cancer (between 72,000 and 89,600 people each year in the UK) experience moderate to severe intensity pain before death, often for many months2,6. Longitudinal studies with cancer patients reveal the pain progression to be dynamic and complex. Pain control is often a trial and error process that requires continuous assessment, education, reassurance and individualized titration of analgesia[[16]](#endnote-17).These patients’ preferred place of care and death is usually home (not hospital) but still many are admitted for improving pain control[[17]](#endnote-18). Evidence indicates that improved cancer pain management is associated with integration of community primary care with palliative care[[18]](#endnote-19),[[19]](#endnote-20). Closer integration of pain management, palliative care, primary care and oncology services is therefore needed to improve pain management for patients with pain related to cancer including advanced diseases[[20]](#endnote-21),[[21]](#endnote-22),[[22]](#endnote-23).

There is evidence to suggest that better management of cancer related pain may also lead to improved length of survival and quality of life[[23]](#endnote-24)both by reducing drug-related morbidity and improving general mobility. Hence, there will be need for better organized services as recommended by the framework for pain services for cancer and life limiting disease published by the Faculty of Pain Medicine in 201918. We noted that 80% of the patients were able to reduce analgesic dose by at least 40% with anticipated reduction in side effects. These results are an improvement on our previous prospective audit10 and probably reflect improved patient selection and technical expertise in performing PCC.

In this audit several patients received the procedure very late in their disease trajectory, and 5 patients out of 25 died within 4 weeks from causes unrelated to PCC. Early referral for PCC assessment appears, therefore crucial to fully exploit the room for improvement in pain control offered by PCC. Earlier referral for assessment would also avoid offering PCC in a desperate situation in a sicker patient with potential for higher procedure-related morbidity. Therefore,we suggest that patients who have pain which may be adequately treatable by PCC should be offered assessment at the earliest opportunity, rather than first progressing through multiple analgesic titrations which is time consuming and may be sub-optimal compared to PCC. In our view, there should be a discussion of alternative management options at the outset in line with UK GMC guidance on consent[[24]](#endnote-25) and Montgomery ruling[[25]](#endnote-26). Evidence suggests substantial morbidity and mortality even in the general population from treatment with high dose opioids combined with gabapentinoids and other adjuvants, a very common combination in our cohort, further supporting this case for early referral[[26]](#endnote-27).It has been shown previously that the PCC procedure carries a low risk when carried out in specialized units 5,6, and our data is consistent with these results13.

We did not see any consistent pattern of improvement in EQ-5D, though there was missing data for the anxiety and depression domain. We suggest that EuroQol, while a good tool for measurement of various health states including chronic pain, may not serve well in measuring the outcomes of a specialized technique (PCC) aimed at pain relief in group of patients with terminal cancer treated with complex pharmacological regimens as in our series. The three EQ-5D dimensions mobility, self-care and usual activities appear to simply not improve in this group, even with excellent pain relief. There was substantial improvement in pain and patients’ need for pain killers. However, interestingly, the overall VAS quality of life scale did not reflect these dramatic positive changes. Our study design prevents us from evaluating the role of very late referral to PCC for the apparent lack of post-PCC QoL changes. It is possible that a prolonged period of experiencing intractable pain and high opioid requirements, on the background of suffering from a terminal illness contributes to creating an ‘entrenched misery’ which is irreversible even with an analgesic procedure as effective as PCC. It is also possible that once pain is removed as the overwhelming negative experience in a person’s life, that the reality of having cancer and the systemic symptoms it brings comes into sharper focus and impacts more on quality of life than previously. The performance of the procedure so late in a person’s illness trajectory may also play a part in this.

We consider the use of personalized goals (e.g. to reduce pain killers, to be able to return home, to go on a holiday) in place of a generic QoL tool may go some way to capture subtle improvements even in this situation. A limitation of our study is that follow up data is only available for 4 weeks – ascertainment of longer follow up periods after PCC is an important gap in the literature, and earlier referral would also facilitate acquisition of such data.

Within the UK, it is important to recognize that the number of centers offering PCC has reduced in recent years. Currently, there are now only three centers (Liverpool, Portsmouth and Glasgow). This has implications for patients with significant morbidity needing to travel substantial distances to be considered for this procedure. Internationally, this decline is also recognized, with cordotomy being considered a ‘dying art’ within North America where the practice of PCC is being infrequently utilized[[27]](#endnote-28). Within the last decade, only three medical centers within the United States have reported on their PCC performance[[28]](#endnote-29). Globally, unless PCC is highlighted as an essential procedure for the management of complex pain, and specific teaching provided within specialist training programmes, expertise may disappear16,17. Additionally, accepting that there may be a limited number of centers offering PCC, assessing innovative methods for consultations (initial screening assessment utilizing telemedicine) would represent a key area for further development to link peripheral services with tertiary care cancer pain MDT services16,17.

Based on our findings we propose that centres involved in the care of patients with end-stage cancer should consider early referral for review of patients with cancer-related unilateral pain below shoulder for their suitability for PCC. Previous consensus work has agreed that PCC should be considered when the patient is requiring strong opioids and/or pain persists or escalates following systemic oncology interventions including radiotherapy and chemotherapy[[29]](#endnote-30).Within the wider literature, the indication for PCC is defined as ‘medically refractory, unilateral pain in a patient with an expected lifespan of less than one year’. With a still rising incidence of mesothelioma in the UK, further recognition of the role of PCC within these patients’ treatment trajectory would seem particularly pertinent.

**CONCLUSIONS**

The present findings support a role of PCC for the treatment of intractable, unilateral cancer related pain from mesothelioma and other cancers. 5 patients died within 4 weeks post PCC due to cancer related illness and thus early referral may have provided a longer period of pain relief from PCC for these patients. Despite excellent pain relief, reduction in analgesia need, and improved patient’s global impression of change, EQ-5D parameters relating to their function and overall quality of life did not improve. Further work is needed to investigate effect of PCC of quality of life and as qualitative research to study patient’s experience of PCC. In addition, work is needed to educate pain specialists, palliative medicine and oncologists on the importance of early referral for PCC.

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