

# Is quality of life improved by neurolytic coeliac plexus block in pancreatic cancer pain management?

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## ABSTRACT

Pancreatic cancer (PC) is a disease of insidious onset and late clinical presentation with an annual incidence of 100 per million population. It is the sixth most common cause of mortality from cancer and records a median survival of about 3–6 months without treatment. Quality of life (QOL) is the major consideration in the management of advanced cancer. PC adversely affects QOL of sufferers and mostly presents with abdominal pain from intra- and extra-pancreatic origins. Opioids are the “Gold-standard” treatment in severe cancer pain management. However, its use may be challenged by debilitating side effects such as drowsiness, respiratory depression, constipation, nausea/vomiting, or opioid toxicity which further worsens QOL of patients burdened with cancer. Neurolytic coeliac plexus block (NCPB) is indicated in PC pain that is resistant or refractive to conventional analgesic methods. Such potent analgesic technique could ease the suffering of cancer patients and provides an improved QOL. Reports indicate that NCPB provides effective analgesia in advanced PC but might be associated with minor and transient side effects such as hypotension, diarrhea, and retroperitoneal hemorrhage. Reports from studies analyzed in this review show that NCPB provides superior analgesia in PC pain management than opioid-based therapies. However, there is no satisfactory evidence that NCPB improved QOL in these patients. This shows that QOL of advanced cancer patients is not synonymous with pain relief. Improvement in QOL will be difficult without management of the “total pain” felt by the patients.

**Key words:** Block, coeliac plexus, pain-management, pancreatic-cancer, quality-of-life

## INTRODUCTION

Pancreatic cancer (PC) is a disease with an insidious onset, and patients usually present late with complaints of jaundice (90%), pain (70%), or intestinal obstructive symptoms.<sup>[1]</sup> In the United-kingdom and United States of America, the annual incidence of PC is approximately 100 per million population; it is the sixth most common cause of death from cancer in these countries.<sup>[2]</sup> A recent report reveals an incidence of about 250,000 new cases of PC annually worldwide.<sup>[3]</sup> It has a poor prognosis with median survival from diagnosis of 3 to 6 months without treatment and 23 months following surgery and adjuvant therapy.<sup>[1]</sup> It is more common in men.

Quality of life (QOL) is the major consideration in advanced cancer pain management.<sup>[4]</sup> It adversely affected by pain associated with PC. Abdominal pain in PC disease could arise from intra- and extra-pancreatic perineural invasion by malignant cells as seen in 71–98% of PC specimens.<sup>[5]</sup> Pain could also result from pressure by local and metastatic lesions, therapeutic interventions, and/or coexisting medical ailments. In addition, emotional, psychological, and spiritual factors contribute to the “total pain” felt by these patients. Therefore, multi-disciplinary management is required to maintain QOL, alleviate suffering and improve coping and adaptation skills among patients burdened by this disease.

The World Health Organization (WHO) recommend opioids as the mainstay of severe cancer pain pharmacotherapy.<sup>[6]</sup> In

severe pain associated with PC, large doses of opioids that might be required could be associated with high incidence of debilitating side effects such as respiratory depression, drowsiness, constipation, nausea/vomiting, and toxicity. These can worsen the clinical state of the patients and necessitate the requirement of alternative analgesic methods with more tolerable side effects. Invasive regional techniques such as neurolytic and non-neurolytic blockade of the coeliac plexus are indicated in patients with pain refractive or resistant to conventional analgesic methods.

Pain stimuli are transmitted from the pancreas to the higher centers through the coeliac plexus. Neurolytic coeliac plexus blockade (NCPB) which interrupts transmission of such noxious stimuli can be achieved by chemical, radiofrequency, or cryo-ablative means. A study recorded complete pain relief in 65% of patients who successfully received NCPB; the remainder had concurrent pain from other somatic and neuropathic sources.<sup>[7]</sup>

NCPB provides effective analgesia with reduced opioid consumption and side effects. Most of its complications such as backache, hypotension, diarrhea, and retroperitoneal hemorrhage are minor and transient; however, severe infrequent complication such as paraplegia<sup>[8]</sup> underpins the importance of meticulous technique and careful patient selection. The safety of this procedure has been improved by the emergence of advanced image enhancement tools such as fluoroscopy, endoscopic

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ultrasound, computed tomography (CT), magnetic resonance, and laparoscopy.

Coeliac plexus blockade using local anesthetics and opioids may be preferred due to their less destructive mechanisms of action. However, relatively short duration of action and the remote location of the coeliac plexus makes their frequent employment less attractive. This review will explore the evidence in literature to justify the use of this form of cancer pain therapy and to determine whether it improves the QOL among users.

## LITERATURE REVIEW AND CRITICAL ANALYSIS

QOL is a broad multidimensional concept that includes subjective evaluation of a patient's general well-being.<sup>[9]</sup> It is difficult to measure and might be based on the physical and occupational functioning, psychological state, social interaction, and somatic sensation experienced by the patient.<sup>[10,11]</sup> Consequently, attempts have been made to assess QOL using tools such as uniscale (numerical rating scale [NRS]), multiple factor evaluation (quality of life questionnaire [QLQ]), multiscale somatic factor, and other functional assessment questionnaires. The multiple factor evaluation questionnaire incorporates all the elements of quality of care. The report shows that "pain score and multiscale psychological or multiscale social factor are not correlated."<sup>[11]</sup> However, components of "QOL" and "total pain" correlate; therefore, a multidisciplinary cancer pain management protocol which addresses all the dimensions of "total pain" is expected to improve the QOL of patients.

Functional well-being is the most important measure of overall satisfaction with life among cancer patients.<sup>[12]</sup> Somatic pain generates a cascade of physiological, psychosocial, and spiritual functional impairment which ultimately aggravates total pain. Cancer of the pancreas has a poor prognosis and presents with severe pain at advanced stages.<sup>[1]</sup> Management aims to ensure that the patient lives as well as possible while avoiding the burden of pain. It is, therefore, pertinent to adopt techniques which provide durable and dependable analgesia with least side effects. Regional analgesic techniques such as neurolytic and non-NCPBs (have been employed in this regard.<sup>[13]</sup>

Neurolytic procedures have been successfully applied in pain management since the early 20<sup>th</sup> century with trigeminal neurolysis by Schloesser in 1903; Kappis performed the 1<sup>st</sup> percutaneous coeliac plexus neurolytic block for pain due to upper abdominal malignancy in 1919.<sup>[14]</sup> Neurolytic blockade is an interruption of impulse transmission from the destruction of neurons by chemical or physical means. Chemical neurolytic substances include alcohol, phenol, and glycerol. Physical neurolytic methods include the use of radiofrequency, laser or cryo-ablative probes, and surgical transection (cordotomy).

Physical techniques and chemical agents have similar mechanisms of action. They produce nerve injury sufficient to cause degeneration of nerve fiber and myelin sheet distal to the point of application (Wallerian degeneration).<sup>[14]</sup> Chemical neurolysis does not completely disrupt the nerve cell; axonal regrowth from the persisting basal lamina of the schwann cells allows reconnection of the proximal end of the damaged nerve fiber. Hence, a temporary interference of impulse transmission is experienced,

which accounts for the average 3 months of analgesia following chemical neurolysis.<sup>[14]</sup> Surgical transection completely disrupts the neuron and basal lamina. This often results in disorganized regrowth without reconnection of the severed neurons with possible production of painful neuromata and dysaesthetic pain.<sup>[15]</sup> This explains the general preference of chemical over surgical neurolysis in cancer pain management. Nerve tissues can be heated or severed by laser probes. Laser disrupts the interior of the neurons which subsequently undergoes Wallerian degeneration. Regeneration can occur from the perineurium if it is not damaged. Similarly, radiofrequency probes use heat generated from electricity to coagulate the neuron; this provides a discrete and controllable heat source whose effect is dependent on the set temperature. Cryo-neurolysis utilizes severe hypothermia (-20°C) at the tip of a probe, generated by rapid expansion of nitrous oxide or carbon dioxide. This can also be achieved by a probe connected to liquid nitrogen. Application of such probes causes ice crystallization of the neurons which results in a prolonged "Wallerian degeneration." Normal neural activity returns in 3-4 months following nerve regeneration if there is no damage to the basal lamina. Radiofrequency probe produces precise neurolysis through a discrete and controllable heat source. This avoids unwanted side effects such as charring, sticking, and injury to contiguous structures.<sup>[7]</sup> However, the diffuse structure of the coeliac plexus makes it unsuitable for NCPB. This is also applicable to laser and cryo-ablative probes.

Pain arising from the abdominal viscera innervated by the coeliac plexus such as pancreas, liver, gall bladder, stomach, and intestines (up to transverse colon) can be relieved by blockade of the plexus. The risk of deafferentation pain from nerve regeneration after NCPB makes the procedure preferable in terminal malignant diseases.<sup>[14,16]</sup> Indications for NCPB include significant PC pain (verbal rating scale >3), intolerable analgesic side effects, and requirements of potent opioids (the WHO step III).<sup>[17]</sup> It is also indicated in cancer pain resistant or poorly responsive to opioids and adjuvant therapy. Abdominal malignancies may present with mixed visceral and somatic pain due to retroperitoneal or metastatic spread.<sup>[14]</sup> Therefore, diagnostic coeliac plexus block with local anesthetics is used to differentiate the pain of somatic origin. Diagnostic block also functions to anticipate the response to neurolytic therapies and guide formulation of treatment plans.<sup>[18]</sup>

Chemical NCPB can be achieved using of 50-100% ethyl alcohol.<sup>[7]</sup> It might cause pain on injection; therefore, 5-10 ml of 0.25% bupivacaine is given before or mixed with ethyl alcohol before use. Ethyl alcohol is the traditionally preferred agent for NCPB because it has less affinity for vascular structures around the coeliac plexus than phenol.<sup>[7,14]</sup> Methyl alcohol solution 20-25ml and 10ml bilaterally is sufficient to achieve NCPB via the retrocrural and anterocrural approaches, respectively. Phenol solution (10%) may also be used for NCPB. A 10 ml solution of phenol is required for neurolysis through the anterocrural approach, it is painless on injection.<sup>[7]</sup> Retrocrural administration is precluded due to large volumes needed. Mechanism and duration of action are similar to alcohol; however, it is less preferred for NCPB due to a higher risk of damage to vascular structures around the coeliac plexus.<sup>[14]</sup>

Complications associated with chemical NCPB include orthostatic hypotension and diarrhea due to pharmacological sympathectomy and backache; these are mild and transient. Other rare side

effects are retroperitoneal hemorrhage due to injury to vascular structure and paraplegia from injury to the feeder arteries of the spinal cord.<sup>[7]</sup> These make a careful selection of patients and meticulous technique mandatory.

The coeliac plexus is located retroperitoneally between the T<sub>12</sub> and L<sub>1</sub> vertebrae, anterior to the diaphragmatic crura bilaterally. It is surrounded by a rich vasculature composed of the abdominal aorta, coeliac, and superior mesenteric arteries.<sup>[7]</sup> Coeliac plexus contains two large ganglia made up of sympathetic fibers (from the splanchnic nerve) and parasympathetic fibers (from vagus nerve). It serves autonomic and sensory functions to most abdominal organs. Percutaneous, intraoperative, and endoscopic ultrasonography-assisted NCPB have been described.<sup>[7,19]</sup> Advanced technology involved in these image-assisted procedures, improves the safety, efficacy, and reduces side effects associated with NCPB.

Several studies have demonstrated the efficacy of NCPB in PC pain management; this is also associated with significant reduction in opioid side effects.<sup>[13,16,19]</sup> These opioid adverse effects and stress from cancer pain reduce the QOL of patients. A study by Mercadante compared the effects of NCPB and opioid therapy on 20 advanced cancer patients.<sup>[20]</sup> In that study, 10 patients received NCPB through the posterior (retrocrual) approach while the rest had morphine per oral. A home palliative care team managed these patients till death to assess and treat complications from analgesic therapy. Visual analog scores showed significantly greater pain relief in both groups compared to baseline values; however, NCPB group enjoyed better but insignificant analgesia. While decrease in total daily opioids consumption was continuous till death in the NCPB group, the reverse was applicable to the oral morphine group. Survival rate was comparable in both groups with 51 ± 26 days and 47 ± 9 days recorded in the NCPB and opioid groups, respectively. The large error of mean suggests the low statistical power of the study. Absence of power calculation and the small study population negatively impacts the validity of the study. Patients who received NCPB recorded fewer side effects compared to those who had opioid therapy. However, non-binding and non-randomization of exposed that study to bias which further reduces its credibility. Moreover, there was no direct QOL assessment in that study.

Another clinical trial by Kawamata *et al.* also compared the effect of NCPB and morphine treatment on QOL in patients with PC pain.<sup>[13]</sup> QOL was assessed before therapy and fortnightly thereafter (primary outcome) with multiple factor evaluation QLQ and performance status scale (NRS). Secondary outcomes were quality of analgesia (measured with visual analog scale [VAS]) and total morphine consumption. Although two groups were demographically similar, the absence of randomization exposed the study to a high risk of selection bias. Patients in the NCPB group had longer survival from admission (95 ± 31 days) compared to the morphine group (74 ± 28 days), but there was no test of significance. The wide error of mean also suggests a small sample size in that study. QOL did not improve statistically after NCPB; however, it deteriorated significantly in the morphine group. Pain relief was significantly better in the first 4 weeks and total weekly morphine consumption was reduced by about 50% throughout the 10 weeks of this study following NCPB. Furthermore, there was a significant increase in the incidence

of anorexia, nausea, constipation, and tiredness in the morphine group. Although a conclusion that NCPB prevented deterioration in QOL compared to morphine analgesia in PC pain management might be reassuring, there was no power calculation to justify the clinical significance. Moreover, the small number of participants jeopardises the general acceptability of results from that study.

A related randomized, double-blind, and controlled clinical trial by Wong *et al.* assessed the effect of NCPB on pain relief, QOL and survival in 100 patients with unresectable cancer of the pancreas.<sup>[21]</sup> Two equally divided groups received either NCPB and sham subcutaneous injection (placebo) or systemic (subcutaneous) morphine and sham intramuscular injection (placebo). The primary outcome measured with NRS was pain relief; this was significantly better after NCPB than systemic opioid ( $P = 0.005$ ). The difference in survival rate between the NCPB (16%) and systemic opioid (6%) groups was not statistically significant. Furthermore, the side effect profiles of both groups were similar. It can be deduced from the report that NCPB qualifies as adjunct therapy since both groups recorded similar total daily morphine consumption throughout the study. QOL was a secondary outcome measured with functional assessment of cancer therapy (FACT)-PC questionnaire. This was also similar in both groups which suggest that pain relief alone does not translate to improvement in QOL. However, this study was statistically powered to assess pain relief and rate of survival only.

Another study by Stefaniak *et al.* compared the effects of NCPB and videothoroscopic splanchnicectomy (VSPL) on pain, QOL, and opioids consumption in advanced cancer of the pancreas.<sup>[22]</sup> 95 patients diagnosed with inoperable carcinoma were in this non-randomized controlled clinical trial. The primary outcome measured with VAS showed comparable analgesia between the NCPB and VSPL groups which were significantly greater than the opioids therapy group (control). However, the gap between assessments (2 weeks after procedure and 8 weeks thereafter) might have been too long, arbitrary and non-reflective of patient's pain status in-between. A weekly assessment could have been more appropriate. QOL was assessed using FACT questionnaire. In general, QOL was significantly improved in the NCPB and VSPL groups compared to control. While there was an improvement in all the components of the functional assessment tool in patients who had NCPB, those in the VSPL group recorded improvements in physical components and fatigue only. Survival rates were similar in the three groups at 2 and 8 weeks. Non-randomization of participants which the authors considered "more ethical" may have biased the selection of participants. The *t*-test which was employed in the data analysis of results requires multiple analyses of the three groups in this study thereby increasing the risk of  $\beta$ -error. Analysis of the results using analysis of variance for parametric data and Kruskal-Wallis test for non-parametric data would have yielded a more credible comparison. The absence of a power calculation for this study further reduces its credibility.

Furthermore, a randomized, blinded, and controlled clinical trial that compared the effect of CT-guided NCPB with opioid analgesia in advanced cancer pain management was reported by Zhang *et al.*<sup>[23]</sup> VAS pain scores were significantly lower in the NCPB group; however, the interval between pain assessment (1, 7, 14, 30, 60, and 90 days) is irregular and might not have

reflected the patient's pain experience. Weekly pain assessment could have been more appropriate. Side effects following intervention were fewer and transient with the NCPB group. QOL (measured with a NRS) was a secondary outcome and was similar in the two groups. Use of NRS in measuring appetite, sleep, and communication is not robust enough to reliably assess QOL following the interventions. A total multiple-factor evaluation tool such as would have yielded better results. Although the sample population seemed fairly adequate, the clinical significance of this study is affected by lack of statistical power calculation.

A Cochrane review in 2011 aimed to determine the efficacy, safety, and adverse effects of different techniques of coeliac plexus neurolysis for inoperable PC pain treatment.<sup>[24]</sup> Six randomized controlled clinical trials which involved 358 patients were included in this review. The outcome measures were analgesia (using VAS), total analgesic consumption and adverse effects of treatments. They reported that coeliac plexus neurolysis was safe and offered significantly greater analgesia at 4 weeks than control (opioids). It also provided significantly reduced total opioid consumption and adverse drug effects than control. Moreover, a meta-analysis by Zhong *et al.* involving seven randomized controlled trial (RCTs) compared the efficacy of NCPB and opioid-based therapy in advanced PC pain management.<sup>[19]</sup> Outcome measures such as analgesia (measured with VAS), total opioid use, and adverse effects of drugs used were uniform in all the trials. The review showed that NCPB provided better analgesia, less drug use, and fewer side effects than opioid-based therapy. However, only 3 RCTs were blinded. Moreover, comparison of the rate of survival between the two interventions was inconclusive due to insufficient data. Furthermore, the effect of both interventions on QOL was not analyzed.

## CONCLUSION

Evidence from literature examined so far shows that NCPB is safe in PC pain management.<sup>[19,24]</sup> No mortality was associated with its use. Commonly associated side effects such as orthostatic hypotension and diarrhea were mild, transient, and controllable. Retroperitoneal hemorrhage and paraplegia were not observed in any of the studies. All the trials confirmed the superior analgesic efficacy of NCPB over opioids therapy alone. However, it is uncertain if the additional opioid use after NCPB was in response to pain from the lesion, metastasis, somatic, coincidental sources, or drug dependence. All the clinical trials (except one) reported significantly reduced opioid consumption and side effects following NCPB.<sup>[21]</sup> Many of the studies were impaired by low study size, no statistical power calculation and non-randomization of the participants which hampered the internal and external validity of their findings.<sup>[13,20-23]</sup> Tools employed in QOL assessments were non-uniform in most of the studies included in that meta-analysis.<sup>[13,21,23]</sup> Moreover, no study was powered to evaluate the quality of care in NCPB for PC pain management.

QOL is not synonymous with pain relief. Reduction in stress due to pain and reduced opioid side effects are expected to improve QOL following NCPB in PC patients. However, none of the studies analyzed showed satisfactory evidence that NCPB improved QOL in these patients. Finally, improvement in QOL will be difficult without the management of the "total pain" felt by the patients.

## RECOMMENDATIONS

Randomized controlled clinical trials that are statistically powered to primarily assess the effect of NCPB on QOL using multiple-factor evaluation tools are recommended. Psychosocial factors may reduce the willingness of patients and their relatives to participate in such a study at such terminal stage of this condition, but adequate education could enhance participation. A geographical cluster of patients with PC pain can also impair the recruitment of enough patients in such a study. A multicenter collaborative study is recommended to address this possible setback and enhance the credibility of the findings.

This review has demonstrated that analgesia alone does not translate to improved QOL of cancer patients. A biopsychosocial approach to PC pain management is, therefore, recommended to achieve an optimal outcome. This requires a multidisciplinary team including physicians from various specialties (such as Palliative care, oncology, chronic pain, anesthesia, and orthopedics), nurses, physiotherapists, psychologists, medical social worker, pharmacists, and chaplain. This will ensure adequate pain management with improved outcome in patients at such a vulnerable stage in life.

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