Archives of Anesthesiology and Critical Care (Autumn 2024); 10(4): 385-391.

Available online at http://aacc.tums.ac.ir

Research Article

Comparison of Splanchnic Nerve Block with Ropivacaine/ Depo Medrol and Ropivacaine/Depo Medrol/Fentanyl in Patients Suffering from Abdominal Pain Due to Pancreatic Cancer

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ARTICLE INFO

Article history:
Received 14 September 2023
Revised 09 October 2023
Accepted 25 October 2023

Keywords:
Splanchnic block;
Pain;
Pancreatic cancer;
Pharmaceutical;
Painkillers

ABSTRACT

Background: This double-blind clinical trial aimed to investigate the effectiveness of splanchnic nerve blocks using different medication combinations on pain severity and duration of pain relief in patients with pancreatic cancer-related abdominal pain.
Methods: Thirty eligible patients were randomly assigned to either a control group receiving splanchnic blocks with Ropivacaine/Depo Medrol/Saline or an intervention group receiving splanchnic blocks with Ropivacaine/Depo Medrol/Fentanyl. Pain severity was assessed using the Numeric Rating Scale (NRS) at 2, 6, and 24 hours and one week post-intervention. Statistical analysis included independent t-tests, Friedman tests, and False Discovery Rate (FDR) correction.
Results: Prior to intervention, no significant difference in NRS scores was observed between groups ($p = 0.0642$). However, at the 6-hour and one-week intervals, the case group exhibited significantly lower NRS scores than the control group, indicating the efficacy of the intervention in reducing pain levels. The case group showed a substantial decrease in NRS scores from a pre-intervention mean of 7.8 to 0.5 at 2 hours, while the control group experienced a reduction from 9.083 to 2.583. The mean duration of pain relief was longer in the case group (5.429 days) compared to the control group (3.25 days). Friedman tests revealed significant differences in pain scores across time intervals within both groups ($p < 0.001$).
Conclusion: Splanchnic nerve blocks using Ropivacaine/Depo Medrol/Fentanyl combination demonstrated significant pain reduction effects, particularly at 6 hours and one-week post-intervention, compared to the control group. These findings showed that the addition of fentanyl in pharmaceutical combination as a opioid to the splanchnic block has reduced the pain score and increase the duration of pain relief in patients being involved in pancreatic cancer with abdominal pain.

The authors declare no conflicts of interest.

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Introduction

The normal pancreas comprises acinar cells that secrete digestive enzymes, ductal cells that secrete bicarbonate, Centro acinar cells that provide a geographical connection between acinar cells and ducts, islets of Langerhans secreting hormones, and relatively inactive stellate cells [1]. Most malignant neoplasms of the pancreas are adenocarcinomas. Rare pancreatic neoplasms include neuroendocrine tumors (which can secrete hormones such as insulin or glucagon) and acinar carcinomas (which can release digestive enzymes into the bloodstream) [2]. Even less common neoplasms encompass cystadenocarcinomas, Pancreatoblastoma, and solid pseudo papillary neoplasms [3]. Pain can be a significant problem for individuals diagnosed with pancreatic cancer [4]. Symptoms of this type of cancer can include abdominal pain that radiates to the back, loss of appetite or unintentional weight loss, skin yellowing and whites of the eyes turning yellow (jaundice), pale stool color, dark-colored urine, skin itching, and blood clotting [5]. These cancers can potentially attack the nerves near the pancreas and exert pressure on them, which can lead to pain in the abdomen or lower back [6]. Chronic abdominal pain is always considered a problem for patients due to the difficulty of achieving effective treatment [7]. Both benign and malignant conditions can lead to chronic abdominal pain. Accurate diagnosis before commencing effective treatment is essential [8]. Chronic abdominal pain is the most common reason for seeking outpatient medical care. Cancer-related pain can have visceral, somatic, or neuropathic nature, and in about 50 percent of cancers, the pain is a combination of these types of pain [9-10]. For most patients, morphine or similar medications (opioids) can assist in pain management [11]. There are numerous drug options available, with opioids being the most common analgesics prescribed for alleviating pain in patients with pancreatic cancer [12]. Since abdominal pain is associated with pancreas parenchymal inflammation, non-steroidal anti-inflammatory drugs (NSAIDs) that target cyclooxygenase (COX) enzymes are often used [13]. In rare cases, local anesthetics (such as prilocaine and bupivacaine) and paracetamol are used [14]. These agents are not without harm and may have side effects such as sedation, respiratory depression, altered bowel movement, sphincter of Oddi spasm, constipation, etc [15]. Prescribing long-acting local anesthetics like ropivacaine or bupivacaine via an epidural catheter is a common approach for pain management during surgery for patients undergoing major abdominal procedures [16]. To enhance the analgesic effects, sufentanil, an opioid analgesic, is added to the local anesthetic. Local anesthetics reveal their analgesic properties by blocking voltage-gated sodium channels. A splanchnic nerve block is an effective method for alleviating chronic pain in the upper abdominal region, often resulting from cancer or pancreas inflammation [17]. The splanchnic nerves are positioned on both sides of the spinal column and transmit pain signals from abdominal organs to the brain. Pancreatic cancer is particularly associated with severe pain and is recognized as one of the most painful malignancies [18]. Sometimes, it may not respond to opioids and other pharmacological treatments. A splanchnic nerve block is a valuable adjunctive treatment for managing abdominal pain associated with gastrointestinal pathology [19]. This study focused on comparing the efficacy and duration of pain relief in patients experiencing abdominal pain due to pancreatic cancer. The study examined the use of splanchnic nerve block in comparison with ropivacaine/ Depo Medrol and ropivacaine/ Depo Medrol /fentanyl combinations.

Methods

This study was a double-blind clinical trial, after obtaining approval from the university's ethics committee, written informed consent will be obtained from patients who meet the study's inclusion criteria. 30 patients will be selected for both the control and intervention groups using a random number table. Initially, researchers will conduct visits with the patients, and their initial demographic and clinical data will be recorded. Splanchnic nerve blocks are performed bilaterally in all patients. An anesthesiologist familiar with random number tables and the research methodology will prepare the drug combination needed for the splanchnic nerve block and provide it to the performing fellow conducting the procedure.

Control: Splanchnic blocks (8ml Ropivacaine (0.2%)+ 1ml Depo Medrol (40mg)+ 1ml Saline.

Intervention: Splanchnic blocks (8ml Ropivacaine (0.2%)+ 1ml Depo Medrol (40mg)+ 1ml Fentanyl (50µg).

The splanchnic nerve block is performed bilaterally by injecting 10 milliliters on each side.

At 2, 6, and 24 hours, as well as one week after injection, using a standardized 10-point scale, a numerical rating score (NRS) for pain was measured in both groups. The NRS ranges from pain-free (score of 0) to the maximum pain imaginable (score of 10), allowing the patient to indicate their pain intensity voluntarily by marking the corresponding point. The severity of pain will be recorded by the collaborating fellow investigator for all patients in both groups, and consistent instructions regarding the use of this measurement tool will be provided to them. Additionally, the duration of pain relief will also be measured.

Sample size

In a double-blind clinical trial study, patients who have pancreatic cancer and are also experiencing abdominal pain will be included in the study. The sample size of the

study population is determined to be 30 individuals based on the pilot study by Liu et al [20]. After meeting the inclusion criteria, participants will be randomly selected.

Inclusion Criteria: 18yr>, life expectancy of more than 3 months, patients with chronic pain due to cancer who are experiencing severe pain, pain intensity of patients classified as moderate to severe based on NRS, willingness to participate in the study.

Exclusion Criteria: history of allergy to narcotics or local anesthetics, substance abuse and alcohol addiction, active skin disease at the site of the nerve block, history of chemotherapy within the last 7 days.

Data analysis

Investigating the Effect of Treatment on Pain Scores and Duration of Pain Relief

In order to compare the feature values between cases and controls, an independent t-test was performed. Additionally, the resulting p-values were adjusted using the False Discovery Rate (FDR) correction. The aim of this analysis was to identify features that exhibit significant differences between cases and controls while accounting for multiple tests.

In this study, our primary aim was to investigate potential variations in Numeric Rating Scale (NRS) scores at different time intervals between two distinct groups: a case group and a control group. The NRS scores served as quantitative indicators of self-reported pain levels at various stages of the treatment process. Within our analysis, we specifically focused on the NRS scores in respective time intervals, including "NRS before score," "NRS after 2 hours," "NRS after 6 hours," "NRS after 24 hours," and "NRS after 1 week."

Comparing Pain Scores Across Different Time Intervals Within Each Group

To compare the reported ordinal pain scores at different time intervals within each treatment group, a non-parametric statistical test known as the Friedman test was conducted. This test is particularly useful when analyzing repeated measurements with ordinal outcomes. The aim was to ascertain whether the pain scores exhibited statistically significant variations across the different time intervals within each group. The resulting Chi-squared statistic and associated p-values provided information about the presence and magnitude of statistically significant differences in pain scores among the time intervals within each group.

Ethical Considerations:

In this study, in addition to obtaining the necessary introduction letters from the ethics committee of Tehran University of Medical Sciences with the code IR.TUMS.NI.REC.1402.003, the following points were considered research ethics and were observed.

Results

Comparative Analysis of Cases and Controls

Presents the distilled outcomes of our analyses, revealing significant differences between cases and controls for various features. Age showed no substantial divergence, with cases (56.4 years) and controls (52 years) exhibiting comparable mean ages. This was confirmed by a p-value of 0.38 and an FDR_bh Q-Value of 0.38.

In the control group, there were a total of 15 participants. Among them, 6 participants were female, while 9 participants were male. This indicates that the majority of participants in the control group were male, with a smaller number of female participants.

In contrast, the treatment group consisted of a total of 15 participants as well. Within this group, 3 participants were female, and 12 participants were male. The 'treatment group had a larger proportion of male participants compared to females.

Effect of splanchnic nerve block on pain severity

In our investigation, we conducted independent t-tests to explore potential variations in Numeric Rating Scale (NRS) scores across distinct time intervals between two primary groups: a case and a control group. These NRS scores were utilized as objective measures of self-reported pain levels at different stages of the intervention process. Our analysis revealed intriguing findings. Initially, prior to any intervention, there were no statistically significant differences in NRS scores between the two groups, although the p-value approached significance (t-statistic = -1.9271, p-value = 0.0642). However, subsequent analyses unveiled noteworthy trends. Notably, while NRS scores at the 2-hour and 24-hour marks did not demonstrate statistical significance, a significant divergence emerged at the 6-hour and 1-week intervals, with the case group exhibiting significantly lower pain scores compared to the control group. These results suggest that the efficacy of the intervention became prominent, particularly after 6 hours, and remained significant even after 1 week of intervention, indicating its potential to reduce reported pain levels.

In the case group, the mean Numeric Rating Scale (NRS) score before any intervention was reported as 7.8 (SD= 1.634), indicating a moderate level of pain on average. Following the intervention, notable reductions in pain scores were observed at various intervals. At the 2-hour mark, the mean NRS score dropped to 0.5 (SD= 1.212), signifying a substantial reduction in pain levels. Similar trends were observed at the 6-hour and 24-hour intervals, with mean NRS scores of 2.0 (SD = 2.0) and 3.5 (SD= 2.609), respectively. The most prolonged impact was evident after 1 week, with a mean NRS score of 5.0 (SD= 2.828). In contrast, the control group, which did not receive the intervention, exhibited distinct patterns of pain scores. The mean NRS score before any intervention in the control group was higher, recorded at

9.083 (SD = 0.933), indicating a relatively higher baseline pain level on average compared to the case group. Following this, the mean NRS scores at the 2-hour, 6-hour, and 24-hour intervals were 2.583 (SD= 2.247), 4.083 (SD= 2.316), and 4.083 (SD= 2.316), respectively. Notably, the control group also experienced reductions in pain scores, albeit to a lesser extent compared to the case group. The mean NRS score after 1 week in the control group was 6.0 (SD= 2.0), suggesting that pain levels remained relatively stable over time.

Effect of splanchnic nerve block on duration of pain relief

The results of our analysis revealed intriguing findings concerning the duration of pain relief. Specifically, the independent t-test conducted for the "Duration of pain relief" variable yielded a t-statistic of approximately 2.0001 and a p-value of approximately 0.0553. While the observed difference in the duration of pain relief between the case and control groups did not reach conventional levels of statistical significance ($p < 0.05$), the proximity of the p-value to this threshold suggests that there may be noteworthy trends deserving further investigation. These outcomes provide valuable insights into the potential impact of splanchnic nerve block on the duration of pain relief in patients with abdominal pain related to pancreatic cancer. the mean duration of pain relief in the case group was calculated to be 5.429 (SD= 3.981), highlighting the sustained effect of the intervention. The mean duration of pain relief in the control group was 3.25 (SD= 3.978), reflecting the natural course of pain without the intervention.

Splenic Block with Ropivacaine/Depomedrol and Ropivacaine/Depomedrol/Fentanyl on Pain Severity across interval intervention

The objective of this investigation was to discern potential variations in pain scores across distinct time intervals within each splanchnic group.

To achieve this, we employed the Friedman test, a non-parametric statistical method tailored for analyzing repeated measures data. For the control group, the Friedman test yielded a Chi-squared statistic of 42.16, accompanied by a notably low p-value of 1.54e-08. Similarly, in the case group, the Friedman test produced a Chi-squared statistic of 49.81, with a p-value of 3.95e-10.

These findings substantiate the existence of statistically significant disparities in pain scores across various time intervals within both groups. The outcomes underscore the importance of considering temporal dynamics when evaluating pain scores within the context of different treatments.

Discussion

Pain is one of the most common and costly health conditions. Acute abdominal pain is the primary symptom and main reason for hospitalization in patients with acute pancreatitis (AP). Splanchnic nerve block alleviates severe abdominal pain caused by pancreatic cancer. This involves a form of nerve disruption that prevents the splanchnic nerve network in the abdomen from transmitting pain signals to the brain.

Our comparative analysis of cases and controls aimed to shed light on the efficacy of splanchnic nerve block in managing pain associated with pancreatic cancer. Firstly, it's noteworthy that age did not significantly differ between cases and controls, with both groups exhibiting similar mean ages, supported by non-significant p-values and FDR_bh Q-Values. Gender distribution in the control group skewed towards males, with 9 male participants and 6 females. Conversely, the treatment group had a greater proportion of male participants, with 12 males and 3 females.

In the assessment of splanchnic nerve block's effect on pain severity, we conducted independent t-tests for Numeric Rating Scale (NRS) scores across various time intervals. While there were no statistically significant differences in NRS scores before intervention, the case group demonstrated significantly lower pain scores at the 6-hour and 1-week intervals, suggesting the intervention's effectiveness. Notably, pain reduction became particularly prominent after 6 hours, emphasizing its sustained impact over time. In contrast, the control group exhibited less pronounced reductions in pain scores, indicating the natural course of pain without intervention. Furthermore, our analysis explored the impact of splanchnic nerve block on the duration of pain relief. Although the difference was not statistically significant, the proximity of the p-value to the threshold suggests potential trends warranting further investigation. The case group demonstrated a mean duration of pain relief of 5.429, underscoring the sustained intervention effect. Meanwhile, the control group exhibited a mean duration of pain relief of 3.25, reflecting the natural progression of pain without intervention.

Regarding the analysis of pain severity across interval interventions within each splanchnic group, the Friedman test confirmed significant variations in pain scores over time in both the control and case groups. These results emphasize the importance of considering temporal dynamics when evaluating pain scores within different treatment contexts.

In a study conducted by Kang et al. [21], It was concluded that no significant difference was observed in the management of herpes zoster (HZ) pain and prevention of post herpetic neuralgia between the observed patients. The occurrence of adverse effects was higher in the RF group compared to the R group.

In the study by Chaudhary et al. [22], they found that adding fentanyl to ropivacaine might result in a shorter complete motor blockade, greater hemodynamic stability, and no increase in side effects.

Dorothee and colleagues [23] reported that 10mg of hyperbaric 0.5% levobupivacaine combined with 5 µg of sufentanil was the most suitable drug combination in terms of pain relief duration.

Chen and colleagues demonstrated in a study in 2020 [24] the superiority of dexmedetomidine over sufentanil for epidural pain relief during childbirth.

In a systematic review conducted by Kirksey and colleagues [25], they demonstrated that buprenorphine, clonidine, dexamethasone, magnesium, and dexmedetomidine are agents suitable for prolonging the effect of local anesthetic peripheral nerve blocks.

The study by Chavan and colleagues [26] in 2019 concludes that adding fentanyl to the local anesthetic in brachial plexus block leads to an increase in the duration of pain relief.

Bundscherer and colleagues [27], conducted a study to investigate the effects of ropivacaine, bupivacaine, and sufentanil on colon and pancreatic cancer cells under laboratory conditions. The results revealed, only high concentrations of ropivacaine or bupivacaine exhibited antiproliferative effects. It appears that the protective effects of epidural anesthesia observed in clinical studies might not be based on the direct effects of these drugs on cancer cells.

Liu and colleagues [20] conducted a study comparing three solutions of ropivacaine/fentanyl for epidural pain relief under patient-controlled conditions after surgery. Their findings indicate that the concentration of the local anesthetic solution at low doses is the primary determinant of motor block with epidural pain relief under patient-controlled conditions after lower abdominal surgery.

Seetha ram KR and colleagues [28], demonstrated in a study that the addition of fentanyl to ropivacaine significantly prolongs the duration of postoperative analgesia with clinically insignificant influence on hemodynamics and motor blockade with minimal side effects.

In the study by Macias, A., and colleagues [29], they found that epidural ropivacaine/fentanyl offers no clinical advantage compared with bupivacaine/fentanyl for post-thoracotomy analgesia.

K Nishikawa and colleagues [30], found that Peripheral application of fentanyl to lidocaine for axillary brachial plexus blockade in this study provided an improved success rate of sensory blockade and prolonged duration.

Our study possesses several strengths that contribute to the robustness and reliability of the findings. Firstly, the utilization of a non-parametric test like the Friedman test for analyzing pain score variations over time within treatment groups adds to the methodological rigor. Additionally, the consideration of false discovery rate (FDR) Q-values helps control for multiple testing and reduces the likelihood of false positives.

Despite the strengths of our study, there are certain limitations that warrant acknowledgment. Firstly, the sample size may impact the generalizability of our findings, particularly if the sample is not representative of the broader population. The reliance on self-reported pain scores could introduce subjectivity and reporting bias. Furthermore, the absence of certain confounding variables in our analyses, such as comorbidities or concurrent treatments, may impact the accuracy of our conclusions.

Our study opens aspects for future research in several directions. Conducting larger-scale studies with diverse populations could enhance the generalizability of our findings. Longitudinal studies that track pain scores and treatment outcomes over extended periods could provide insights into the durability of treatment effects. To establish causal relationships, randomized controlled trials with carefully controlled variables are recommended. Exploring additional variables, such as psychological factors or treatment adherence, could yield a more comprehensive understanding of pain management. Moreover, incorporating advanced statistical techniques, such as machine learning algorithms, could uncover hidden patterns and relationships within the data. Collaborations with multi-disciplinary teams could facilitate a more holistic interpretation of the results and their clinical implications.

Conclusion

Splanchnic nerve blocks using Ropivacaine/Depo Medrol/Fentanyl combination demonstrated significant pain reduction effects, particularly at 6 hours and one-week post-intervention, compared to the control group. These findings showed that the addition of fentanyl in pharmaceutical combination as a opioid to the splanchnic block has reduced the pain score and increase the duration of pain relief in patients being involved in pancreatic cancer with abdominal pain.

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