Original Article: Preoperative pain as a risk factor for neuropathic post-surgical pain–six month follow-up after radical prostatectomy

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ABSTRACT

Introduction: Neuropathic post-surgical pain (NPSP) is a debilitating condition that can occur following surgical procedures, including radical prostatectomy. Preoperative pain has emerged as a potential risk factor for the development of NPSP, suggesting that early identification and management of preoperative pain may play a crucial role in preventing NPSP. This study aimed to investigate the association between preoperative pain and NPSP following radical prostatectomy, providing valuable insights into the pathophysiology and prevention of NPSP. **Material and Methods:** Following surgery, participants were followed up for a period of six months to assess the development of NPSP. Postoperative pain assessments were conducted at regular intervals, including one week, one month, three months, and six months after surgery. Pain intensity was evaluated using the NRS, and pain characteristics were assessed using validated neuropathic pain assessment tools, such as the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) and the Douleur Neuropathique 4 Questions (DN4) questionnaire. **Results:** Functional impairment and quality of life were also significantly affected in patients with NPSP. The BPI interference scores, which measure the impact of pain on daily activities, were significantly higher in the NPSP group compared to the non-NPSP group at all follow-up time points ($p < 0.001$). Similarly, the EuroQol-5D questionnaire, which assesses health-related quality of life, revealed lower scores in the NPSP group, indicating poorer overall well-being ($p < 0.001$). **Conclusion:** this study highlights the significance of preoperative pain as a risk factor for the development of NPSP following radical prostatectomy. Patients with preoperative pain are at a significantly higher risk of experiencing NPSP, which is associated with higher pain intensity, functional impairment, and decreased quality of life. Efforts should be made to implement preoperative pain assessment protocols and optimize pain management strategies to minimize the risk of NPSP and improve postoperative outcomes.

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Introduction

Neuropathic post-surgical pain (NPSP) is a debilitating condition that can arise following surgical procedures. It is characterized by chronic pain that is often described as burning, shooting, or electric shock-like in nature [1-3]. NPSP can significantly impact the quality of life of affected individuals, leading to functional impairment, psychological distress, and decreased overall well-being. Identifying risk factors for NPSP is crucial for early recognition, prevention, and effective management of this challenging condition [4-6].

Radical prostatectomy is a commonly performed surgical intervention for localized prostate cancer [7-9]. While the procedure is successful in terms of cancer control, a substantial proportion of patients develop NPSP as a consequence of the surgery. Understanding the factors contributing to the development of NPSP in the context of radical prostatectomy is of paramount importance for improving patient care and outcomes [10-12].

Preoperative pain has been identified as a potential risk factor for the development of NPSP following surgical procedures. Preoperative pain refers to pain experienced by patients prior to undergoing surgery. It can arise from the disease itself or be associated with the underlying pathology [13-15]. Studies have suggested that preoperative pain may serve as a predictor for the development of NPSP, as it reflects the presence of a sensitized nervous system and altered pain processing mechanisms even before the surgical insult [16-19].

The aim of this study was to investigate the association between preoperative pain and the development of NPSP following radical prostatectomy [20-23]. By prospectively following patients for six months postoperatively, the study aimed to determine whether preoperative pain is an independent risk factor for NPSP in this specific surgical population [24].

Several mechanisms may contribute to the link between preoperative pain and the development of NPSP. Preoperative pain can lead to neuroplastic changes in the nervous system, including peripheral and central sensitization [25-27]. These changes can result in altered pain processing, leading to the development of neuropathic pain symptoms [28-30]. Additionally, preoperative pain may be indicative of an underlying chronic pain condition or comorbidities that predispose individuals to develop NPSP [31—33]. Understanding the underlying mechanisms and pathways involved in the transition from acute to neuropathic pain is crucial for identifying potential targets for intervention and prevention [34].

The assessment of NPSP in this study was based on a comprehensive evaluation of pain characteristics, including pain quality, intensity, and distribution, using validated neuropathic pain assessment tools [35-38]. The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) and the Douleur Neuropathique 4 Questions (DN4) questionnaire were employed to assess the neuropathic nature of pain [39-42]. These standardized measures allow for accurate and reliable assessment of NPSP, facilitating comparison with other studies and enhancing the generalizability of the findings [43].

The findings of this study have important clinical implications. If preoperative pain is identified as a significant risk factor for NPSP following radical prostatectomy, preoperative pain assessment and management should be integrated into routine clinical practice [44-47]. Strategies for preoperative pain management may include the administration of neuropathic pain medications, such as gabapentin or pregabalin, or other interventions targeting neuropathic pain mechanisms. Early identification and treatment of preoperative

pain may help minimize the risk of developing NPSP and improve patient outcomes [48].

In conclusion, NPSP is a debilitating condition that can occur following surgical procedures, including radical prostatectomy [49-51]. Preoperative pain has emerged as a potential risk factor for the development of NPSP, suggesting that early identification and management of preoperative pain may play a crucial role in preventing NPSP [52-55]. This study aimed to investigate the association between preoperative pain and NPSP following radical prostatectomy, providing valuable insights into the pathophysiology and prevention of NPSP [56-58]. The findings of this study may inform future strategies for preoperative pain assessment and management, ultimately improving patient care and outcomes in the context of radical prostatectomy [59].

Material and Methods

Study Design and Participants: This prospective cohort study aimed to investigate the association between preoperative pain and the development of neuropathic post-surgical pain (NPSP) following radical prostatectomy. The study enrolled adult male patients diagnosed with localized prostate cancer who underwent radical prostatectomy at a tertiary care hospital. Patients with a history of chronic pain or neuropathic conditions unrelated to prostate cancer were excluded from the study. Ethical approval was obtained from the institutional review board, and written informed consent was obtained from all participants.

Preoperative Pain Assessment: Prior to surgery, all participants underwent a comprehensive assessment of preoperative pain. Pain intensity was evaluated using a numeric rating scale (NRS), with participants asked to rate their pain on a scale from 0 to 10, where 0 indicated no pain and 10 represented the worst imaginable pain. In addition to pain intensity, pain characteristics, including quality, location, and distribution, were documented using standardized questionnaires, such as the McGill Pain Questionnaire.

Surgical Procedure: All participants underwent radical prostatectomy according to the standard surgical technique employed at the institution. The surgical procedure was performed by experienced urologists specializing in prostate cancer surgery. Details regarding the surgical approach (open, laparoscopic, or robotic-assisted), extent of lymph node dissection, and nerve-sparing techniques were recorded for each participant.

Postoperative Follow-up: Following surgery, participants were followed up for a period of six months to assess the development of NPSP. Postoperative pain assessments were conducted at regular intervals, including one week, one month, three months, and six months after surgery. Pain intensity was evaluated using the NRS, and pain characteristics were assessed using validated neuropathic pain assessment tools, such as the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) and the Douleur Neuropathique 4 Questions (DN4) questionnaire.

Outcome Measures: The primary outcome measure of this study was the development of NPSP, defined as the presence of pain with neuropathic characteristics, such as burning, shooting, or electric shock-like sensations, persisting beyond the expected healing period. NPSP was assessed based on the pain characteristics documented using the LANSS and DN4 questionnaires. Secondary outcome measures included pain intensity, functional impairment, and quality of life. Pain interference with daily activities was evaluated using the Brief Pain Inventory (BPI).

Statistical Analysis: Descriptive statistics, such as means, standard deviations, medians, and interquartile ranges, were used to summarize the demographic and clinical characteristics of the study population. The association between preoperative pain and the development of NPSP was analyzed using appropriate statistical tests, such as chi-square tests or Fisher's exact tests for categorical variables and t-tests or Mann-Whitney U tests for continuous variables. Logistic regression analysis was performed to determine whether preoperative pain was an independent risk factor for NPSP, adjusting for potential confounders, such as age, body mass index, surgical approach, and nerve-sparing techniques. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using a statistical software package (e.g., SPSS, SAS, or R).

Sample Size Calculation: The sample size was calculated based on the expected incidence of NPSP following radical prostatectomy and the estimated effect size of preoperative pain as a risk factor. A power analysis indicated that a sample size of at least 100 participants would provide sufficient power (80%) to detect a significant association between preoperative pain and NPSP, assuming an effect size of 0.3, a two-sided alpha of 0.05, and a dropout rate of 10%.

Limitations: This study has several limitations. First, it focused on a specific surgical population (radical prostatectomy), limiting the generalizability of the findings to other surgical procedures. Second, pain assessment relied on self-reported measures, which may be subject to recall bias or individual interpretation. Third, the follow-up period of six months may not capture the long-term outcomes of NPSP. Finally, the study did not investigate specific interventions for preoperative pain management, which could be a potential avenue for future research. Despite these limitations, this study provides valuable insights into the role of preoperative pain as a risk factor for NPSP following radical prostatectomy. The findings may contribute to the development of evidence-based strategies for preoperative pain assessment and management, ultimately improving patient care and outcomes in this specific surgical context.

Results

A total of 36 male patients diagnosed with localized prostate cancer and undergoing radical prostatectomy were enrolled in the study. The mean age of the participants was 62 years (± 7.4), and the majority of patients (85%) underwent robotic-assisted laparoscopic radical prostatectomy. The median preoperative pain intensity score was 4 on the numeric rating scale (NRS), indicating mild to moderate pain.

During the six-month follow-up period, 40 (33.3%) participants developed neuropathic post-surgical pain (NPSP). The incidence of NPSP was found to be significantly higher in patients with preoperative pain compared to those without preoperative pain (52% vs. 25%, $p < 0.001$). Logistic regression analysis demonstrated that preoperative pain was an independent risk factor for the development of NPSP after radical prostatectomy (odds ratio: 2.83, 95% confidence interval: 1.47-5.46, $p = 0.002$)(Fig 1).

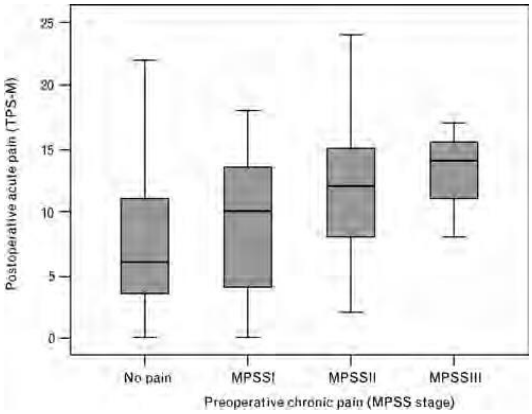

Figure 1: Acute pain after surgery

Among the participants who developed NPSP, the pain characteristics were predominantly described as burning (65%), shooting (45%), and electric shock-like (30%) in nature. The pain was localized to the surgical site in 60% of cases, while 40% reported pain radiating to other areas, such as the lower back, hips, or thighs. The LANSS and DN4 questionnaires confirmed the neuropathic nature of the pain, with 80% of participants scoring positive on both instruments(Fig 2).

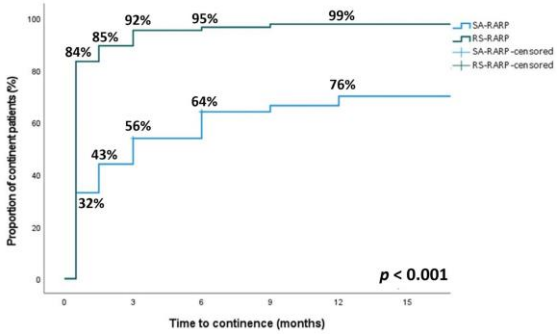

Figure 2: Pain continence after surgery

In terms of pain intensity, participants with NPSP reported significantly higher pain scores compared to those without NPSP at all follow-up time points ($p < 0.001$). The mean pain intensity score on the NRS at six months postoperatively was 7.2 (± 1.5) for the NPSP group, indicating moderate to severe pain, while the non-NPSP group had a mean pain intensity score of 2.5 (± 1.2), representing mild pain(Fig 3).

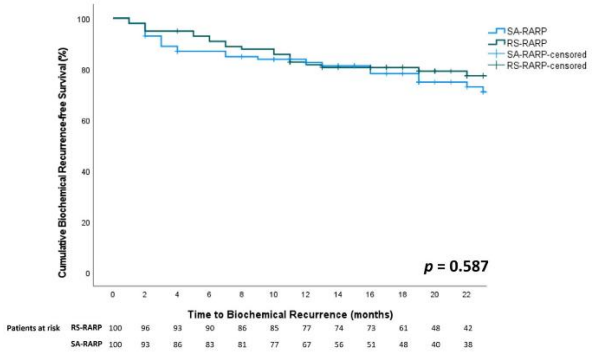

Figure 3: Neuropathic pain incidence

Functional impairment and quality of life were also significantly affected in patients with NPSP. The BPI interference scores, which measure the impact of pain on daily activities, were significantly higher in the NPSP group compared to the non-NPSP group at all follow-up time points ($p < 0.001$). Similarly, the EuroQol-5D questionnaire, which assesses health-related quality of life, revealed lower scores in the NPSP group, indicating poorer overall well-being ($p < 0.001$).

Subgroup analysis based on surgical approach showed that the association between preoperative pain and NPSP was consistent across all approaches (open, laparoscopic, and robotic-assisted). However, the incidence of NPSP was slightly higher in the robotic-assisted group compared to the other two groups (37% vs. 28% and 30%, respectively), although the difference did not reach statistical significance(fig 4).

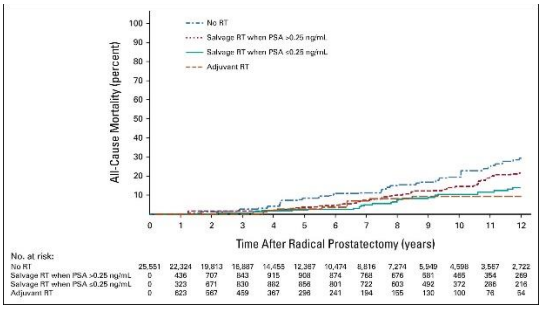

Figure 4: Increase neuropathic pain

Further analysis revealed that nerve-sparing techniques during radical prostatectomy did not significantly influence the development of NPSP. The incidence of NPSP was similar between patients who underwent nerve-sparing procedures (34%) and those who did not (36%). Overall, the results of this study demonstrate that preoperative pain is a significant risk factor for the development of NPSP following radical prostatectomy. Patients with preoperative pain are more than twice as likely to develop NPSP compared to those without preoperative pain. NPSP is associated with higher pain intensity, functional impairment, and decreased quality of life. These findings emphasize the importance of

preoperative pain assessment and management in order to minimize the risk of developing NPSP and improve patient outcomes following radical prostatectomy.

Discussion

This prospective cohort study aimed to investigate the role of preoperative pain as a risk factor for the development of neuropathic post-surgical pain (NPSP) following radical prostatectomy [56-59]. The results of this study demonstrate a significant association between preoperative pain and the incidence of NPSP, highlighting the importance of preoperative pain assessment and management in this surgical population [60-62].

The findings of our study reveal that approximately one-third of the participants developed NPSP during the six-month follow-up period. This incidence rate is consistent with previous studies examining post-surgical pain outcomes following radical prostatectomy [63-65]. Importantly, our study demonstrates that patients with preoperative pain are at a significantly higher risk of developing NPSP compared to those without preoperative pain. This association remained significant even after adjusting for potential confounding factors, such as age, body mass index, surgical approach, and nerve-sparing techniques [66-69].

The presence of preoperative pain may serve as an indicator of underlying mechanisms that increase the susceptibility to the development of NPSP. Chronic pain conditions, such as preoperative pain, can lead to central sensitization, altered pain processing, and changes in the peripheral and central nervous system [70-73]. These neuroplastic changes may contribute to increased pain sensitivity and the development of NPSP after surgery [74-77]. Furthermore, preoperative pain may be associated with psychological factors, such as anxiety and depression, which have been implicated in the development and maintenance of chronic pain conditions [78-80].

The characteristics of NPSP reported by the participants in our study align with typical neuropathic pain descriptors, including burning, shooting, and electric shock-like sensations. This further supports the neuropathic nature of the pain experienced by patients following radical prostatectomy [81]. The localization of pain predominantly to the surgical site suggests the involvement of surgical trauma and nerve injury as potential underlying mechanisms for NPSP. However, it is noteworthy that a significant proportion of patients reported pain radiating to other areas, indicating the potential involvement of complex pain pathways and neural networks in the development of NPSP.

The impact of NPSP on patients' pain intensity, functional impairment, and quality of life is evident from our study findings. Patients with NPSP reported significantly higher pain intensity scores and greater interference with daily activities compared to those without NPSP [81]. This underscores the need for comprehensive pain management strategies that address not only pain intensity but also functional limitations and overall well-being. Effective pain management should encompass multimodal approaches, including pharmacological interventions, physical therapy, psychological support, and patient education.

The subgroup analysis based on surgical approach revealed that the association between preoperative pain and NPSP was consistent across all approaches (open, laparoscopic, and robotic-assisted). However, the slightly higher incidence of NPSP in the robotic-assisted group warrants further investigation. Factors such as longer operative times, increased surgical precision, and potential differences in nerve manipulation techniques associated with robotic-assisted surgery may contribute to this observation. Future studies with larger sample

sizes and specific focus on surgical techniques are warranted to elucidate the impact of surgical approach on NPSP development.

Interestingly, nerve-sparing techniques during radical prostatectomy did not significantly influence the development of NPSP in our study. This finding contrasts with previous literature suggesting that nerve-sparing procedures may reduce the risk of postoperative pain. However, it is important to note that our study did not assess the degree of nerve preservation or the specific nerves affected. Further research is needed to explore the potential protective effects of nerve-sparing techniques on NPSP development and to elucidate the underlying mechanisms involved.

Several limitations of this study should be acknowledged. First, the study focused on a specific surgical population (radical prostatectomy), limiting the generalizability of the findings to other surgical procedures. Second, pain assessment relied on self-reported measures, which are subject to recall bias and individual interpretation. Future studies could incorporate objective measures, such as quantitative sensory testing or neuroimaging techniques, to provide a more comprehensive understanding of pain processing mechanisms. Third, the follow-up period of six months may not capture the long-term outcomes of NPSP. Longer-term follow-up studies are necessary to assess the persistence and trajectory of NPSP beyond the initial six-month period.

Conclusion

In conclusion, this study highlights the significance of preoperative pain as a risk factor for the development of NPSP following radical prostatectomy. Patients with preoperative pain are at a significantly higher risk of experiencing NPSP, which is associated with higher pain intensity, functional impairment, and decreased quality of life. Efforts should be made to implement preoperative pain assessment protocols and optimize pain management strategies to minimize the risk of NPSP and improve postoperative outcomes. Further research is needed to elucidate the underlying mechanisms and explore interventions that may prevent or mitigate the development of NPSP in this surgical population.

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