

Clinical Pain Research

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Does lumbar spinal decompression or fusion surgery influence outcome parameters in patients with intrathecal morphine treatment for persistent spinal pain syndrome type 2 (PSPS-T2)

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Abstract

Objectives: Intrathecal morphine pump (ITMP) infusion therapy is efficient in managing chronic pain refractory to standard treatment. This study evaluates pain relief and improvement of quality of life in chronic pain patients after intrathecal morphine pump implantation for treatment of persistent pain after lumbar spinal fusion surgery and lumbar spinal decompression alone.

Methods: Forty three chronic pain patients that received an ITMP at our department between 2009 and 2019 were retrospectively analyzed divided into 2 cohorts (lumbar spinal fusion surgery and lumbar spinal decompression alone). Pain intensity was evaluated using the numeric rating scale (NRS), quality of life was assessed by EQ-5D-3L, mental health was assessed by Beck Depression Inventory (BDI-V), and Pain Catastrophizing Scale (PCS). Morphine dosage was assessed over time. Data was collected preoperatively, 6 and 24 months postoperatively. Statistical analysis was performed using Friedman's analysis of variance to evaluate the development of NRS, PCS, BDI and EQ-5D-3L over time and Mann-Whitney-U-test for the differences between these parameters in the different cohorts. A two-sided p-value <0.05 was considered statistically significant.

Results: Median age was 64 years (IQR^{25–75} 56–71 years). NRS, EQ-5D-3L, BDI-V, and PCS showed a significant overall improvement after 6 and 24 months compared to baseline data ($p < 0.001$). No statistically significant differences between patients with lumbar spinal fusion surgery and lumbar spinal decompression alone were seen. Furthermore, no statistically significant differences for age and gender were seen. The initially administered median morphine dosage was significantly higher in the fusion group (3.0 mg/day; IQR^{25–75} 1.5–4.2 mg/day) compared to the decompression-alone group (1.5 mg/day; IQR^{25–75} 1.0–2.6 mg/day); ($p = 0.027$).

Conclusions: This retrospective study showed that ITMP have a major long-term impact on pain relief, improve the quality of life, psychological distress, as well as pain catastrophizing in patients with chronic pain following lumbar spinal surgery independent of the previous surgical procedure. After ITMP implantation initial median morphine dosage seems to be significantly higher after spinal fusion compared to decompressive surgery alone.

Keywords: intrathecal opioids; intrathecal drug delivery systems; chronic lumbar pain; persistent spinal pain syndrome-type 2 (PSPS-T2); quality of life; psychological distress

Introduction

Persistent or recurrent pain syndromes with impaired function following spinal surgery are common, affecting between approximately 20 and 40 % of patients, that should be managed in an interdisciplinary environment [1–3]. Despite radiologically successful surgical outcomes, some patients still suffer from pain and impaired function, which can lead to the development of chronic pain syndromes [4]. Chronic pain syndromes after spinal surgical procedures are a frequent cause of intractable pain and are described as Persistent Spinal Pain Syndrome type 2 (PSPS-T2) [5–9].

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Despite advances in conservative and minimal-invasive treatment approaches, there are still patients that remain in significant pain [10–13]. More invasive treatments dependent on the underlying cause of the chronic pain. In some cases reoperation may be indicated [14]. For appropriately selected patients with chronic low back pain, neuromodulation should be considered [10, 15–17]. Most patients take continuous oral analgesics with an increase of the daily dose, which can lead to side effects or ineffective pain control. In 10 %–30 % of patients treated for chronic pain, adequate analgesia with oral analgesics is not obtained [18]. Intrathecal drug delivery systems are an established interventional pain management modality and offer an effective therapy over oral analgesics for the treatment of these patients [19–21]. Morphine has been considered as one of the standard drugs for intrathecal medication [22]. The medication is delivered directly into the subarachnoid space to the site of action on the dorsal horn of the spinal cord while bypassing first-pass metabolism effects and the blood–brain barrier. Through direct delivery a lower effective dose is allowed and less interaction with systemic receptors leads to a decrease of systemic side effects [23–25]. Intrathecal morphine pumps (ITMP) are most common used in patients with spine and non-spine-related pain disorders [20, 26]. ITMPs should also be considered in those patients who are unsuitable or unresponsive to neuromodulation therapy and still warrant further treatment [27]. ITMPs are indicated as a last resort therapy if other conservative measures have failed for at least 6 months [12, 28]. Although many clinical trials have verified the safety and effectiveness of these systems, patients with different underlying conditions report varying treatment success [12, 29]. Thus, it is mandatory to keep in mind, that chronic pain syndromes, regardless of its associated physical pathology are multidimensional influenced by psychosocial factors [20]. Those patients have a low health-related quality of life and high psychological morbidity and are frequent users of health services [7, 30]. Conservative treatment for lumbar pain thus has been extended to multimodal pain therapy, a combination of medical, physical and psychological treatment [31, 32].

In this study, we conducted a retrospective chart review of patients with chronic pain syndromes following lumbar decompression surgery alone and lumbar decompression surgery plus fusion, who had received an ITMP after multimodal therapy. Analyses focused on the clinical condition of patients after implantation and on a variety of clinical outcome scores related to the intrathecal morphine infusion treatment processes. Further, this study evaluates pain relief and improvement of quality of life. To the best of our

knowledge, an in-depth comparison of treatment outcome in PSPS-T2 patients has not yet been published.

Materials and methods

Data collection and outcome measures

A retrospective cohort study of 43 patients treated between 2009 and 2019 with refractory chronic low back pain after spinal surgery was conducted at our neurosurgical department. The cohorts were divided into lumbar spinal decompression alone and lumbar spinal fusion surgery with decompression, and lumbar fusion alone. Patients who received both, decompression and fusion surgery, were included in the group of spinal fusion surgery. After a positive trial phase, the implantation of an ITMP (SynchroMed II, Medtronic®, Minneapolis, Minnesota, USA) with an intrathecal catheter (Ascenda, Medtronic®, Minneapolis, Minnesota, USA) was performed. The management protocol was approved by the Institutional Research Ethics Board (AZ165/14). All patients had received conventional pharmacological treatment including multimodal pain therapy (non-steroidal anti-inflammatory drugs, opioids, and co-adjuvants) in specialized centers or through local pain therapists as well as physical therapy. Personal data, diagnoses, duration of disease, type and number of spinal surgery, and pain medication were assessed at baseline. Pain intensity was assessed using the numeric rating scale (NRS) [33], quality of life by EQ-5D-3L questionnaire [34, 35], and mental health was assessed by Beck Depression Inventory (BDI-V) [36] and Pain Catastrophizing Scale (PCS) [37]. The EQ-5D-5L health index score was calculated first by mapping the EQ-5D-5L health profiles to the EQ-5D-3L profiles using an algorithm developed by van Hout et al. [38]. Questionnaires were completed by all patients preoperatively, 6 and 24 months postoperatively. Further the median morphine dosage in the first 4 weeks postoperatively and in the follow-up after 6 and 24 months, respectively, was assessed.

Intrathecal drug application trial period

A trial was done before implanting the pump to determine the success of intrathecal morphine. Our internal protocol provides the insertion of a lumbar drain under sterile conditions. Afterwards intrathecal morphine testing was performed with initially 0.5 mg and afterwards 1.0 mg. Additionally placebo and 0.25 % carbostesin were applied to complete the test trial. During this process all patients were cardiopulmonary monitored. If the patient had a benefit over the trial, a fully implanted system was implanted at a second operation with intravenous anesthesia (TIVA) and intubation. The definition of successful pain relief was >50 % reduction in NRS and no side effects.

Intrathecal pain pump implantation procedure

The implanted systems were either 20- or 40-ml Medtronic SynchroMed® II pumps (Medtronic®, Minneapolis, Minnesota, USA) with a constant but variable flow rate. The pumps were placed in the lower quadrant of the abdomen, which is an area large enough to accommodate the pump. Surgery was done with intravenous anesthesia (TIVA)

and intubation. Patients were positioned in the lateral decubitus position. All patients received a single dose of intravenous antibiotics pre-operatively. Inpatient stay was 3–5 days.

Follow up visits

The pump refill procedure was done in our outpatient clinic. Refills were generally done using a sterile needle inserted through the skin of the abdomen. This outpatient setting further gave the opportunity to adjust the daily flow rate if necessary. Pumps will signal with a beeping noise if the amount gets below 2 mL. The devices also sound alarms if there is a malfunction, or, for versions with a battery, if the battery runs low (generally after 6–7 years). In case of battery depletion, the implant will be replaced under general anesthesia. Standard administration of the intrathecal medication occurred via continuous infusion, as programmed by the clinician, with dose adjustments made as needed at outpatient clinic visits to maximize efficacy and tolerability.

Statistical analysis

All statistical evaluations were performed with SPSS statistics 24 (IBM corp, Armonk, USA) and Excel (Microsoft Corp., Redmond USA). Descriptive statistics were initially applied to all measures. Treatment success was defined as a long-term pain relief and improvement of quality of life maintained during the whole follow-up period. The data are expressed as median and interquartile range [IQR^{25–75}] or as percentage. Statistical analysis was performed using Friedman's analysis of variance to evaluate the development over time of NRS, PCS, BDI and EQ-5D-3L and Mann-Whitney-U-test for the differences between these parameters in the different groups. A two-sided p-value <0.05 was considered statistically significant.

Results

The cohort consisted of 43 patients (25 females, 18 males) with a median age of 64 years (IQR^{25–75} 56–71 years). Demographic data and diagnoses are summarized in Table 1. Twenty one patients with chronic low back pain that had been prior treated by lumbar spinal decompression surgery and 22 patients with prior spinal fusion surgery were examined. Median disease duration was 4 years. Patients that were treated by spinal fusion and decompression surgery were also counted to the spinal-fusion-group. Three patients were lost to follow-up.

Table 1: Baseline characteristics of the study participants.

Characteristics	
Median age, years	64 (IQR ^{25–75} 56–71)
Male/female (n=)	18/25
Lumbar spinal decompression alone (n=)	21
Lumbar spinal fusion surgery and decompression and lumbar fusion alone (n=)	22

Pain intensity (Numeric rating scale, NRS) at baseline, after 6-and 24-months after ITMP-implantation in the decompression-alone and spinal-fusion group

The median NRS value in the decompression-alone-group improved from 10.0 (IQR^{25–75} 9.0–10.0) to 6.5 (IQR^{25–75} 4.0–7.0) at the 6-months follow-up and to 5.5 (IQR^{25–75} 3.0–7.0) at the 24-months follow-up. The spinal-fusion-group improved from an initial median NRS of 9.0 (IQR^{25–75} 8.0–10.0) to 6.0 (IQR^{25–75} 6.0–7.0) at 6 months and to 6.0 (IQR^{25–75} 6.0–7.0) at 24 months. The improvement of NRS was highly significant in both groups (p<0.001) (Figure 1).

EQ-5D-3L at baseline, after 6-and 24-months after ITMP-implantation in the decompression-alone and spinal-fusion group

The median EQ-5D-3L-score prior to ITMP implantation in the decompression-alone-group was at 0.18 (IQR^{25–75} 0.10–0.34) indicating a highly reduced quality of life. This value improved to 0.57 (IQR^{25–75} 0.31–0.71) at the first follow-up at 6 months, further to 0.61 (IQR^{25–75} 0.18–0.75) after 24-months follow-up. The median EQ-5D-3L-score prior to ITMP implantation in the spinal-fusion-group was 0.24 (IQR^{25–75} 0.16–0.36) and improved to 0.61 (IQR^{25–75} 0.39–0.74) at 6-months follow-up. After 24 months median value remained at 0.61 (IQR^{25–75} 0.42–0.75). Both groups had a highly statistically significant improvement in quality of life on the EQ-5D-3L questionnaire (p<0.001) (Figure 2).

Beck depression inventory (BDI-V) score at baseline, after 6 and 24 months after ITMP-implantation in the decompression-alone and spinal-fusion group

The median baseline score on the BDI-V questionnaire for the decompression-alone-group before treatment was 17.0 (IQR^{25–75} 10.5–27.0) and improved to 5.5 (IQR^{25–75} 0.50–27.5) at 6 months and to 8.0 (IQR^{25–75} 0–17.0) after 24 months. The spinal-fusion-group reported a median value of 12.0 (IQR^{25–75} 4.25–25.0) at baseline and improved to 7.0 (IQR^{25–75} 0.25–19.75) at 6 months and to 7.0 (IQR^{25–75} 1.0–15.75) at 24 months. Both groups had a highly statistically significant improvement (p<0.001) (Figure 3).

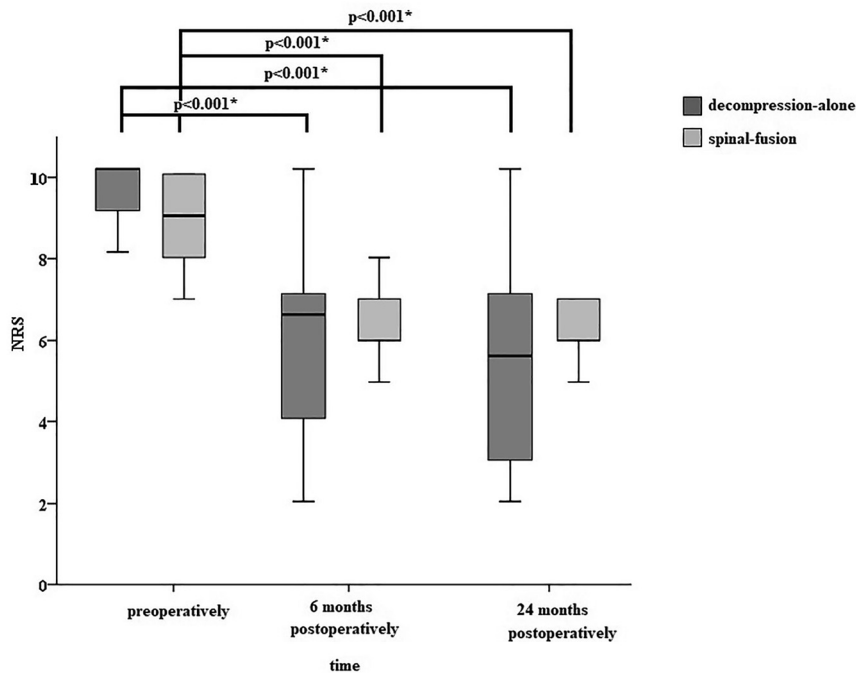


Figure 1: Box plots of NRS at baseline, 6 and 24 months postoperatively.

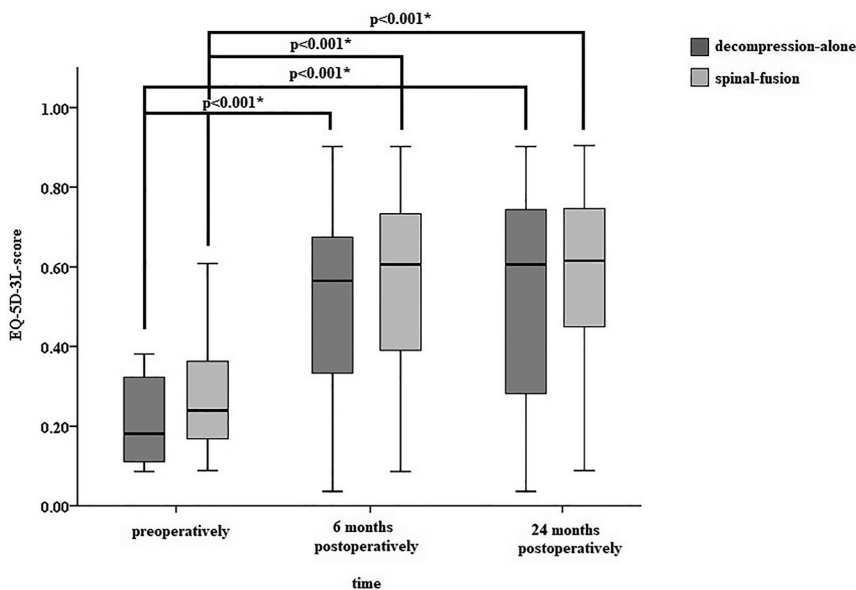


Figure 2: Box plots of EQ5D3L at baseline, 6 and 24 months postoperatively.

Pain catastrophizing scale (PCS) at baseline, after 6 and 24 months after ITMP-implantation in the decompression-alone and spinal-fusion group

At baseline the decompression-alone-group had a median PCS-value of 40.0 (IQR^{25–75} 20.75–48.75) which improved to a value of 20.5 (IQR^{25–75} 8.5–23.75) after 6 months

postoperatively and further to 16.0 (IQR^{25–75} 10.0–44.0) at the 24-months follow-up. The spinal-fusion-group had a median value of 34.5 (IQR^{25–75} 26.5–47) before treatment. An improvement to 22.5 (IQR^{25–75} 18.25–35.25) at 6 months postoperatively and further to 20.0 (IQR^{25–75} 14.75–26.5) after 24 months was seen, respectively. All improvements were statistically significant in both groups at 6-and 24 months ($p < 0.001$) (Figure 4).

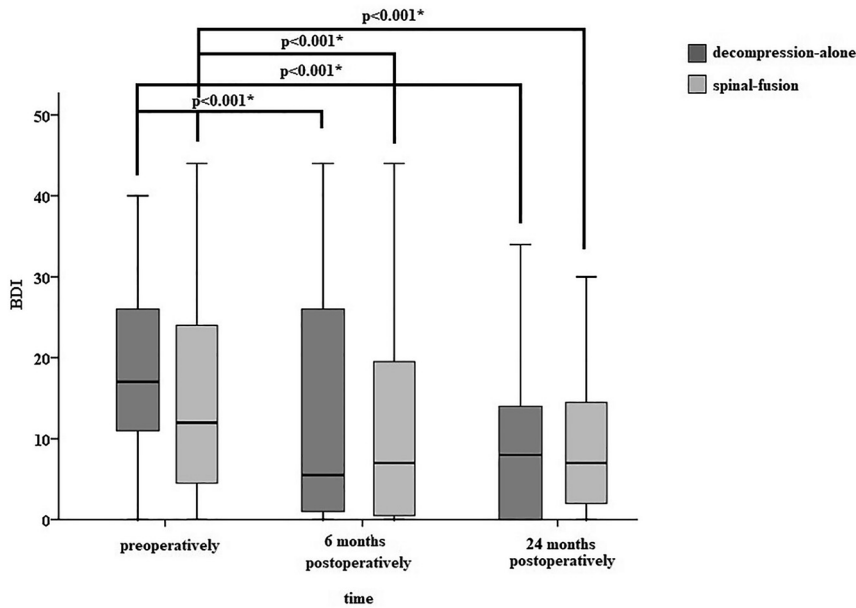


Figure 3: Box plots of BDI-V at baseline, 6 and 24 months postoperatively.

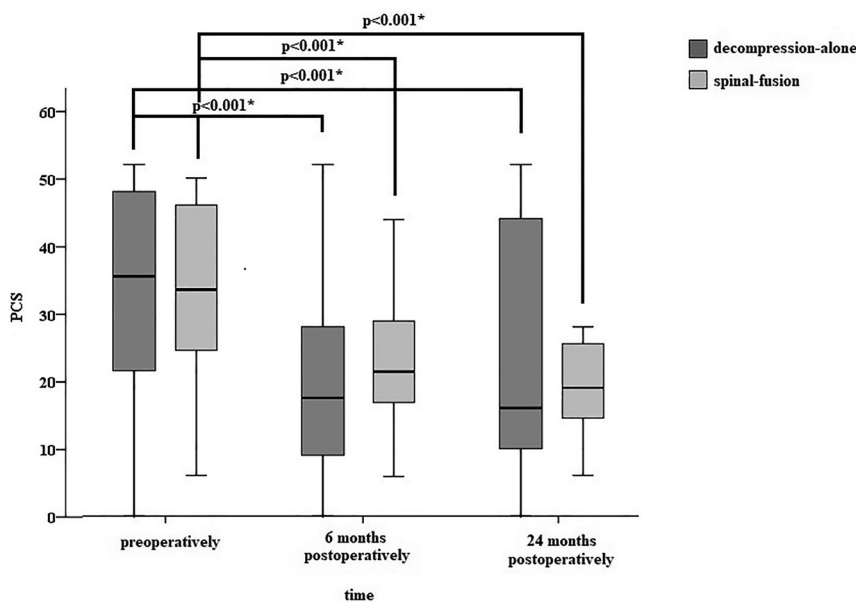


Figure 4: Box plots of PCS at baseline, 6 and 24 months postoperatively.

Differences in NRS, EQD5L, BDI-V, and PCS in the decompression-alone and spinal-fusion group

The comparison of NRS differences in the decompression-alone and spinal-fusion group between baseline values and the values after 6-months and 24-months postoperatively revealed a tendency to higher improvement in spinal decompression group ($p=0.079$ and $p=0.071$). EQ-5D-3L values showed no statistically significant differences between the two groups at 6 months ($p=0.694$) and at 24 months ($p=0.882$). BDI-V values showed no significant differences between the

two groups at 6 months ($p=0.775$) and 12 months ($p=0.184$); (Figure 5). Furthermore, the PCS-score did not show any significant differences 6 and 24 months after ITMP-implantation ($p=0.514$ and $p=0.884$).

Comparison between different age groups and gender

There were no statistically significant differences in NRS, EQ-5D-3L, BDI-V, and PCS for different age and gender in both groups ($p>0.05$).

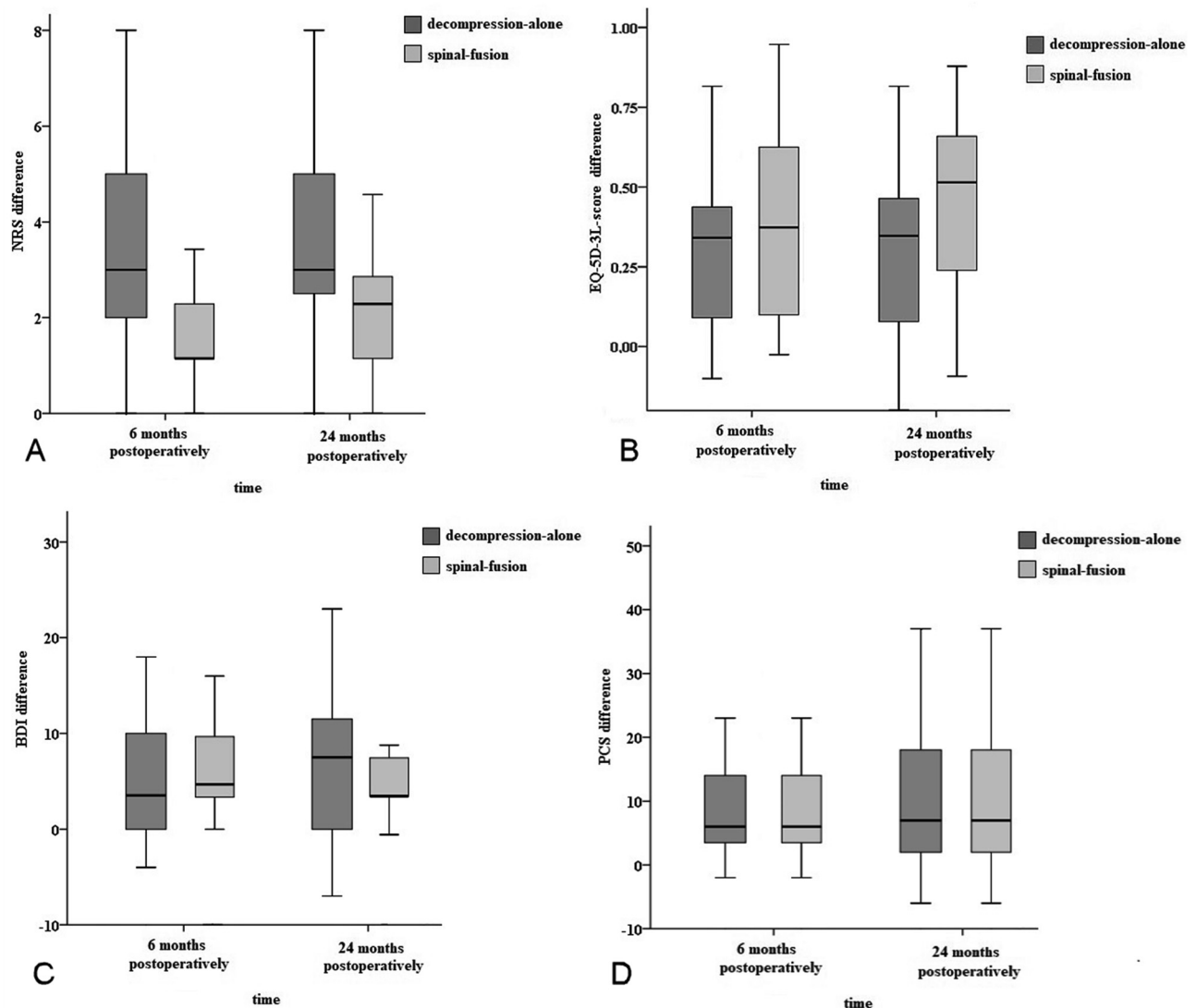


Figure 5: Differences in median of NRS (A), EQD5L-3L (B), BDI-V (C), and PCS (D) in the decompression-alone and spinal-fusion group after 6 and 12 months follow up compared to baseline data showed no significant differences. A two-sided p -value <0.05 was considered statistically significant.

Morphine dosage

After successful trial phase, the ITMP was implanted and drug administration initiated. Directly after implantation morphine starting dose was between 1.0 and 1.5 mg/day. In the whole cohort median morphine dosage initially administered 4 weeks after ITMP implantation was 2.25 mg/day (IQR^{25–75} 1.40–3.05 mg/day); after 6 months, it was 4.45 mg/day (IQR^{25–75} 2.88–6.13 mg/day). In long-term observation after 2 years median morphine dosage was 5.10 mg/day (IQR^{25–75} 2.88–9.13 mg/day). The initially administered median morphine dosage was significantly higher in the spinal-fusion group 3.0 mg/day (IQR^{25–75} 1.5–4.2 mg/day) compared to the decompression-alone group 1.5 mg/day (IQR^{25–75}

1.0–2.6 mg/day); ($p=0.027$). After 3 and 24 months there were no significant differences.

Complications

Total complication rate was 7.14 %. Over the study period of 24 months there were 3 complications that needed hospitalization of the patients. One patient suffered from a wound healing disorder. Another patient had a catheter dislocation which needed to be revised surgically. One patient had symptoms of opioid overdose which was treated by dosage reduction under cardiopulmonary monitoring.

Discussion

This study investigates the influence of intrathecal morphine therapy on various outcome parameters in patients with chronic low back pain following lumbar spinal fusion surgery or lumbar spinal decompression alone. Even after successful spine surgery, patients can still suffer pain and impaired function, which can lead to the development of a postoperative chronic pain syndrome [1, 3, 4, 9]. ITMPs are a therapy option if other conservative measures have failed for at least 6 months, but are only indicated as a last resort therapy [12, 28]. In our study we could achieved a significant NRS improvement in the short-as wells as long-term follow up after 2 years in the lumbar spinal fusion and lumbar spinal decompression alone cohort, respectively. NRS tended to a higher improvement in the spinal decompression cohort. *Brown* et al. described the overall success rate using intrathecal drug devices to manage low back pain at 3 years to be fairly good. Functional improvement among patients was only shown to be minimal [39]. In contrast, *Deer* et al., like in our study, found statistically significant improvements in numeric pain ratings, Oswestry functional scores, and high satisfaction with the therapy at 6-and 12-month follow-up [40]. *Winkelmüller* et al. achieved a benefit in 74.2 % of the patients with intrathecal opiate therapy in chronic low back pain. Average pain reduction after 6 months was 67.4 % [41]. *Lara* et al. reported an improvement of the quality of life measured by SF-36 and in all dimensions of the treatment of pain survey in 30 patients with chronic low back pain after spinal surgery. Intrathecal infusion of morphine is seen as a useful and safe tool for long-term treatment of chronic non-malignant pain [42]. Our results are in accordance with these studies, but we go further comparing two subgroups of lumbar spinal fusion and lumbar spinal decompression, respectively. Both cohorts had a statistically significant improvement in NRS and quality of life on the EQ-5D-3L questionnaire. The differences in NRS and EQD5L in the decompression-alone and spinal-fusion cohort did not show any significant differences. *Tomycz* et al. reported about dual-modality management of patients with PSPS-T2 using a combination of an intrathecal opioid pump and spinal cord stimulator with improved their quality of life [43]. In contrast to this study our patients used only one modality (ITMP), which leads to more consistency and comparability. Furthermore, our results state clearly a significant improvement of all outcome parameters in the whole follow-up. Patients with chronic low back pain may have comorbid factors with psychological disorders [44, 45]. *Celestin* et al. see psychological factors as important predictors with greater risk of poor postoperative outcome

in the interventional treatment of chronic low back pain [46]. Further pain interference shows an association with a new onset of different mood disorders [44]. We see high interest to address these factors as they are crucial for satisfying results. In this study both cohorts showed preoperatively highly elevated scores in BDI-V and PCS, which improved statistically significant at 6-and 24 months compared to the baseline data. The differences in BDI-V and PCS in the decompression-alone and spinal-fusion cohort did not show any significant differences. Our outcome data suggest that intrathecal treatment had a significant impact on pain, function, and psychological distress among study patients independently whether decompression-alone and spinal-fusion was performed. *Duarte* et al. analyzed 20 patients with chronic pain symptoms. 60 % suffered from PSPS-T2. Statistically significant improvements were observed for pain intensity, coping, depression, quality of life, housework, mobility, sleep, and social life [47]. Intrathecal morphine therapy is also seen helpful in improving psychosocial function in patients with intractable pain that had failed to respond to standard multimodal analgesic therapy [48]. These results correspond to our findings, but our study provides a larger and homogenous study sample with patients only dealing with PSPS-T2. Furthermore, we compared two subgroups (lumbar spinal fusion and lumbar spinal decompression) with the most common operative spinal procedures.

Additionally, no statistically significant differences in NRS, EQ-5D-3L, BDI-V, and PCS for age and gender were seen in neither group. *Deer* et al. did also not see these two variables as predictive factors as they had no statistically significant impact on trial success [40]. Interestingly, *Kleinmann* et al. found a difference regarding gender. Only 66 % of analyzed women had a pain reduction of more than 50 %, in men 85 % was achieved [49].

Concerning the intrathecal morphine application, median morphine dosage in the first 4 weeks after ITMP implantation was significantly higher in the spinal-fusion group (3.0 mg/day, IQR²⁵⁻⁷⁵ 1.5–4.2 mg/day) compared to the decompression-alone group (1.5 mg/day, IQR²⁵⁻⁷⁵ 1.0–2.6 mg/day; $p=0.027$). In the follow-up time there were no significant differences in both cohorts. To the best of our knowledge and after careful literature review, we did not find any study dealing with this concern. The morphine dosage compared to the beginning of the ITMP therapy increased over time. After 24 months median daily dosage was 5.10 mg/day (IQR²⁵⁻⁷⁵ 2.88–9.13 mg/day). *Kumar* et al. showed in patients who had received intrathecal morphine for longer than 2 years an increase in morphine dosage to more than 10 mg/day [50]. Our patient cohort's daily median

morphine dosage was lower and significant pain reduction as well as improvement of quality of life was still achieved. In relation to complications our total complication rate was 7.14 % and stood in accordance with the current literature [51, 52].

There were several limitations of the present study. First of all, there was the retrospective character of the study with the well-known shortcomings of this study design. Further the study population was very small, so that a selection bias cannot be excluded.

In summary, we conclude, that ITMPs are a therapy modality that has to be kept in mind for patients dealing with serious not well circumscribed chronic low back pain, if other conservative treatment modalities have failed and neuromodulation is not suitable. The follow-up denotes that this effect is stable over this time. An initially clear etiology of the patient's pain should be determined, high risk factors recognized, and conservative measures exhausted before deciding to go into revision surgery. A multidisciplinary approach is preferred after determining the cause of the chronic pain [53].

Conclusions

This retrospective study showed that ITMP have a major long-term impact on pain relief, improvement of quality of life, reducing psychological distress, as well as pain catastrophizing in patients with chronic pain following lumbar spinal surgery independent of the previous surgical procedure. After ITMP implantation median the initial morphine dosage seems to be significantly higher after spinal-fusion- compared to decompressive surgeries alone. The medical indication for ITMP treatment in chronic low back pain has to be an individual decision.

Research ethics: Approved by the Institutional Research Ethics Board (AZ 165/14). The research related to human use complies with all the relevant national regulations, institutional policies and was performed in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' Institutional Review Board or equivalent committee.

Informed consent: Informed consent has been obtained from all individuals included in this study.

Author contributions: F.P.S.: study design, data analysis, and manuscript creation. R.R.: data collection and patient recruitment. J.N.: data analysis and manuscript review. H.G.: manuscript review. E.U.: manuscript review. M.K.: study design, data analysis, and manuscript review.

Competing interests: M.K. receives honoraria for speaking at symposia from Medtronic®. F.P.S. is enrolled in an

educational program of Medtronic®. The other authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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