Orignial Article

Dexamethasone as Adjuvant to Ropivacaine in Wound Infiltration for Postoperative Analgesia following Spinal Surgery: A Randomized, Double-Blinded, Controlled Trial

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BACKGROUND: Pain following spinal surgery can limit early mobility and increase the risk of chronic pain. Intraoperative wound infiltration by local anesthetics for postoperative analgesia has been widely performed.

OBJETIVE: This study aims to assess the analgesic effects of dexamethasone as an adjuvant to ropivacaine in wound infiltration after lumbar surgery.

PATIENTS AND METHODS: In this study, we randomly assigned sixty patients undergoing lumbar laminectomy and/or osteosynthesis into two groups of 30 patients each. The control group (r-group) received only Ropivacaine in the wound infiltration, while the intervention group (RD-group) received ropivacaine with the addition of dexamethasone .Both groups were administered patient-controlled analgesia (PCA) with morphine for self-medication.

RESULTS: Postoperatively, a blinded evaluator assessed pain at hour 0 (H0), recorded the assessment of surgical wound pain using the visual analog scale (VAS) at 4, 6, 12, 24, and 48 hours, as well as the time to the first opioid request, cumulative morphine consumption, opioid-related side effects, and length of stay. The RD-group had significantly lower VAS scores for postoperative pain within 24 hours compared to the R-group (P<0.005). However, no significant difference was observed between the two groups for pain reported at 48 hours. The RD-group exhibited significantly lower opioid requirements within the first 48 hours (P<0.001) and a significantly longer time to first analgesic demand of PCA compared to the control group (P<0.05).

CONCLUSION: Our study suggests that the addition of dexamethasone to ropivacaine in wound infiltration for patients undergoing lumbar laminectomy and/or osteosynthesis can lead to a reduction in morphine consumption, improved analgesia, and a shorter length of hospitalization.

KEYWORDS: Adjuvant therapy, Dexamethasone, Postoperative analgesia, Spinal surgery.

INTRODUCTION

Lumbar surgery is a common treatment for patients with persistent pain and functional impairment that have not responded to conservative therapies. However, postoperative pain that results from damage to soft tissues and muscles near the surgical site causes discomfort and even lead to chronic pain.[1] This moderate to severe pain is a result of the release of inflammatory mediators secondary to incisional injury.[2] It leads to the activation of the peripheral nociceptors and leads to abnormal action potential transmitted within afferent Ad and C-fibers.[3,4] Glucocorticoids, due to their powerful anti-inflammatory properties, have been suggested as a potential option to prevent or reduce postoperative pain.[5,6] Unfortunately, there are currently no guidelines for the management of post-spinal surgery pain. Patient-controlled analgesia (PCA) is the most common method of pain management,[2,7] but systemic opioids, which are often used as the mainstay of treatment, have many adverse effects, such as nausea, vomiting, confusion, urinary retention, sedation, respiratory depression and pruritus,[8] and that can result in inadequate pain relief. Therefore, identifying ideal multimodal pain management options is crucial for improving postoperative care for spinal surgery patients.

Local anesthetics' wound infiltration has been reported as a simple, safe, and efficient technique in various surgical procedures, and its effects can be enhanced with the use of adjuvants.[9] Dexamethasone, a highly potent, long-acting glucocorticoid, has been shown to improve analgesia, decrease morphine consumption, and antagonize the inflammatory reaction.[9] While single-injection parietal infiltration is well-documented in various surgical procedures,[10] the analgesic effectiveness of a single injection infiltration of the lumbar spine scar after laminectomy and/or osteosynthesis is still under debate.

Thus, this study aimed to assess the analgesic effects of

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dexamethasone as an adjuvant along with ropivacaine in wound infiltration following lumbar surgery.

PATIENTS AND METHODS

Study design

We performed a randomized, controlled, double-blinded trial, over the course of a year, from July 2020 to July 2021, at Fattouma Bourguiba Monastir University Hospital's neurosurgery operating room to evaluate the analgesic effects of dexamethasone used as an adjuvant to ropivacaine in wound infiltration following lumbar surgery. The study was authorized by the Institution's Ethics committee. Written, informed consent was gathered from all patients.

Patient confidentiality and privacy were strictly maintained throughout the study. The study enlisted patients aged 18 years or older with a physical status American Society of Anesthesiologists (ASA) I or II and diagnosed with lumbar disc herniation, lumbar spinal stenosis or lumbar degenerative spondylolisthesis requiring surgical treatment such as lumbar laminectomy and/or lumbar osteosynthesis. Patients with altered communication capacity, previous spinal surgery, neuropathic pain, allergy to opioids, dexamethasone, or local anesthetics, active infection or tumor history, traumatic injury, chronic use of steroids or opioids, severe kidney, hepatic, or pulmonary failure, delayed extubation in post-anesthesia care unit (PACU), major bleeding during or after surgery, or surgical revision within the first 24 hours were excluded from the study. Prior to surgery, patients were taught how to evaluate the incisional pain. Visual analogue scale (VAS) where 0 represents no pain and 10 represents the worst imaginable pain was used. All surgical and anesthetic procedures were performed by the same team of neursurgeons and anesthetists.

Sample size

The study's sample size and power analysis were conducted using the "BiostatTGV" application, taking into account various published reports.[9-11] Based on a target reduction of 30% in postoperative pain intensity, an 80% study power, and a level of significance of $p=0.05$, a minimum sample size of 60 patients was required. Therefore, the enrolled patients were randomly assigned into two thirty-patients groups. The intervention group received wound infiltration with a combination of ropivacaine and dexamethasone, while the control group received wound infiltration with ropivacaine and normal saline.

Study procedure

Sixty patients were eventually recruited. Every individual was randomly allocated to either the study group or the control group. The study group (n=30) received an infiltration of ropivacaine and dexamethasone (RD-group) before wound suture during surgery. Meanwhile, the control group (n=30) was administered ropivacaine and normal saline as wound infiltration (R-group).

All patients in both groups received morphine PCA postoperatively with a bolus of 1mg/1ml and a lockout interval of 7 minutes. No patients were lost during the 3-month postoperative follow-up. The same surgeon's team performed the open surgery, and the same anesthetic team used the same protocol for the general anesthesia procedure. All patients had to fast for two hours for clear fluids while fasting six hours for solid foods.

In the operating room, all patients were monitored and given intravenous general anesthesia induction with remifentanil 0.20ug/kg in 1 minute, propofol 2.5mg/kg, and cisatracurium 0.15mg/kg. Anesthesia was maintained by remifentanil 0.20ug/kg/min, Propofol 6mg/kg/h in an electric syringe pump, and cisatracurium 0.03mg/kg every 20 minutes. The patients were in a prone position. By the end of the intervention, all patients received 1g of paracetamol and 20mg of nefopam intravenously. The investigator was responsible for preparing the preemptive infiltration, and the anesthetist, nurse, surgeon, and participant were blinded.

The surgeon injected a total of 22 ml of the infiltration into each level at the end of the intervention. The infiltration was injected in the subcutaneous tissue and paravertebral muscles, along the posterior area around the spinous process, lamina, transverse process, and facet joints on each side of the surgical wound. In the control group, patients received 150mg of ropivacaine 7.5% (20ml) added to 2ml of normal saline in the wound infiltration. In the intervention group, patients received 150mg of ropivacaine 7.5% (20ml) added to 8mg of dexamethasone in the wound infiltration. After surgical closure, patients were reinstalled in a supine position, and the PCA was set up. An independent observer (blinded anesthesiologist) noted the postoperative pain at H0. The assessment of surgical scar pain was conducted using the visual analogue scale (VAS) as an assessment tool at 4, 6, 12, 24, and 48 hours postoperatively, and these measurements, along with other study points, were noted by a blinded observer, the neurosurgery night shift doctor. The study continued for 48 postoperative hours and up to the third month after surgery, during which the investigator contacted all patients by phone to check for chronic pain transition. Patients were assigned to two groups using an online random generator available on the website http://www.miksi.fr Each patient was assigned a number from 1 to 60 and then integrated into the random generator associated with the number of groups to be created. This program allowed us to generate two groups of 30 patients each, randomly allocated.

Outcome assessment

The primary outcome of the study was the time of the first PCA requirement, which was recorded and documented. The resting VAS scores at 4, 6, 12, 24, and 48 hours postoperatively were also assessed by the patients after they had recovered from anesthesia. The total amount of morphine consumption was documented, and any side effects, such as urinary retention, bradycardia, respiratory depression, hypotension, mental confusion,

and postoperative nausea and vomiting, were noted. The study also monitored for steroid-induced complications, such as wound hematoma or impaired wound healing, as secondary outcomes. Duration of hospitalization after surgery and patient satisfaction assessed by the satisfaction scale were recorded when leaving the hospital. Additionally, chronic pain assessment at 3 months after surgery was evaluated as a secondary outcome.

Statistical analysis

The statistical analysis was conducted using the statistical packages for social sciences (SPSS) version 22.0 program. Descriptive statistics were utilized to express quantitative variables as either the mean ± standard deviation or the median and range, depending on the distribution. Qualitative variables were expressed in numbers and percentages. The analysis of variance (ANOVA) test and t-student test were employed for comparative analysis of continuous variables, while the Chi2 test was used for qualitative variables. Significance was determined by a p-value of <0.05.

RESULTS

Descriptive analysis

During the study period, 94 patients were scheduled for spinal surgery. Thirty-four patients were excluded, leaving a final sample size of 60 patients who were enlisted in the study and have been randomly assigned into two groups of 30 patients each **(Fig. 1)**. Mean age of the patients was 45 years ± 12.03, with a range from 20 to 69 years. The male-to-female sex ratio was 1.7. Of the patients, 48 (80%) had a body mass index (BMI) less than 30, and 12 (20%) had a BMI greater than or equal to 30. According to the ASA physical status classification system, 35 patients (58%) were classified as ASA I and the remaining 25 (42%) as ASA II. Among this population, 35 patients (58%) had no significant medical history. The most common chronic conditions were diabetes (n=9; 15%), high blood pressure (n=8; 13.3%), hypothyroidism (n=4; 6.7%), dyslipidemia (n=2; 3.3%) chronic obstructive pulmonary disease (COPD) (n=2; 3.3%), and pulmonary tuberculosis (n=1; 1.7%). The average time of diagnosis and follow-up for the current pathology was 26.72 months, with a range from 18 days to 56 months. Out of the patients who were included in the study, 29 (48.33%) were scheduled for lumbar laminectomy and 31 (51.66%) were scheduled for lumbar osteosynthesis. Among them, 29 patients (48.33%) had a single level planned for surgery, while 31 (51.66%) had two levels. The mean incision length was 12±1.9 cm, and the mean duration of the intervention was 3.5± 1.08 hours. During the operative procedure, no patients presented any post-infiltration incidents such as intravascular passage, hypotension, conduction disorders, or arrhythmia.

Analytical results

The RD-group and the R-group were similar in terms of patients' demographic features and basic characteristics like age, gender, body mass index, diagnosis, duration of surgery, intraoperative blood loss, and wound length. No significant differences were observed between the two groups **(Table 1).** The resting VAS scores for postoperative low back pain reported by patients were significantly lower in the RD-group than those in the R-group at all suggested assessment times (at 4, 6, 12, and 24 hours postoperatively), with p < 0.005. However, at the 48th hour, VAS scores were comparable between both groups. Furthermore, the first press on PCA morphine was significantly earlier in the R-group (180± 18.9 min) than in the RD-group (360 ± 15 min). Consequently, the cumulative dose of morphine consumption in the RD-group was significantly lower than that in the R-group (p <0.001). In addition, the side effects of opioids such as nausea, vomiting, urinary retention were less frequent in the study group, although the difference was not of statistical significance. Postoperative heart rate and blood pressure, assessed at different times, were similar in both groups. The average length of hospital stay after surgery was 4.17 days in the R-group, compared to 3.17 days in the RD-group, with significant difference between the groups (p = 0.0003). Before leaving the recovery room, patients were asked to complete a satisfaction score, which indicated greater satisfaction in the RD-group compared to the control group, with a significant difference observed between them. Three months after surgery, screening for chronic pain transition revealed that only two patients in the R-group developed chronic pain. No significant difference between the two groups were found.

DISCUSSION

Lumbar laminectomy and/or lumbar osteosynthesis have been widely used to treat degenerative lumbar spine disorders such as stenosis of lumbar canal, spondylolisthesis, and disc herniation, and have been associated with good clinical outcomes and high patient satisfaction.[8,9] However, despite its effectiveness, surgery often results in severe postoperative pain that can significantly impact the patient's quality of life and recovery.[13,14] This is likely the result of extensive dissection of soft tissues, bones, and ligaments required during lumbar surgery, which causes considerable postoperative pain that can be moderate to severe and often lasting 3 days.[2]

Effective management of acute postoperative pain is crucial to accelerate early postoperative rehabilitation,[14] and prevent the onset of secondary chronic pain,[15] which can have long-term effects on the patient's quality of life.[16] Therefore, management of postoperative pain should be integrated into a multimodal analgesia approach that combines pharmacological agents and interventional methods such as locoregional analgesia techniques.[17] Postoperative pain following spinal surgery is caused by the activation of several mechanisms, including nociceptive, inflammatory, and neuropathic pathways.[17,18] Inflammatory pain occurs through mediators such as

cytokines and is characterized by four signs: pain, heat, erythema, and swelling.[18] Inflammatory pain typically lasts for hours to days and is usually reversible.

Wound infiltration using local anesthetics has become an important aspect of multimodal pain management.[16] It has been shown to improve patient comfort and reduce recovery time in various surgical subspecialties.[9-11]

Table 1: Patients characteristics

		RD-group n=30	R-group n=30	p value
Gender	Male	21 (52.5%)	19 (47.5%)	0.610
	Female	9 (45%)	11 (55%)	
Age in years		45,16 ± 12	43,9 ± 8,02	0.569
BMI		27.07±2,66	29,85±4.08	0.754
Chronic diseases	Diabetes	05 (55.5%)	04 (44.4%)	0.923
	High blood pressure	03(37.5%)	05 (62.5%)	0.536
	Hypothyroidism	1 (25%)	03 (75%)	0.631
	Dyslipidimia	2 (100%)	0(0%)	0.129
	COPD	2(100%)	0(0%)	0.234
	Pulmonary tuberculosis	0(0%)	1(100%)	0.109
ASA	I	19 (54.3%)	16 (45.7%)	0,477
	II	11 (44%)	14 (56%)	
Diagnosis	LDH	10(45.45%)	12(54.54%)	0,789
	LDS	11(45.83%)	13(54.16%)	
	LSS	9(64.28%)	5(35.71%)	
Planned operative- act	Laminectomy	15(51.72%)	14(48.28%)	0.666
	Arthrodesis	15 (48.39%)	16(51.61%)	
Operation time minutes		169,5±26.3	174±25.6	0.360
Intraoperative blood loss (ml)		300 ± 50	320± 40	0.414
Incision length (cm)		10 ± 05	9 ± 03	0.289

COPD: Chronic obstructive pulmonary disease; LDH: lumbar disc hernia; LDS: lumber disc stenosis; LSS: spondylosthesis.
ASA: American Society of Anesthesiologists; BMI: Body mass index.

Ropivacaine, a local anesthetic with long-lasting effects and lower toxicity, has been recommended for use in wound infiltration to manage postoperative pain in spinal surgery by the procedure specific postoperative pain management (PROSPECT) group.[19-21] This technique is relatively simple and does not require precise anatomical identification of nerve pathways.[22]

The benefits of wound infiltration techniques, both as single injections or continuous infusions, have been highlighted in the latest expert recommendations for the management of postoperative pain by the French society of anesthesia and resuscitation (SFAR).[23]

In addition, use of local anesthetics have been proven to reduce local ischemic phenomena, which are strongly involved in the genesis of parietal pain, due to their vasomotor properties.[24,25] Furthermore, local anesthetics have anti-inflammatory effects that help limit the phenomenon of pain self-perpetuation at the same level of the peripheral lesion, which can prolong the parietal genesis of the painful messages (peripheral hypersensitization).[26] Ropivacaine, an amino amide local anesthetic, has been the focus of intense interest since its

clinical introduction in 1996 because of its higher safety profile in the central nervous system and cardiovascular system compared to bupivacaine.[27] The maximum recommended dose for single injection infiltration analgesia is 225 mg.[28,29]

Thus, the induction of sufficient and prolonged analgesia still remains a challenging every-day task for clinicians. Several published studies in recent years have demonstrated the efficacy and safety of several adjuvants.[30-32] in prolonging the length of the analgesic effect of local anesthetic while reducing its doses to limit adverse effects.[33,34] Dexamethasone is an economical synthetic glucocorticoid that has a powerful anti-inflammatory effect with a long half-life of 36 to 72 hours. Several randomized controlled trials evaluating the analgesic effects of adding dexamethasone to local infiltration have concluded that dexamethasone as an adjuvant to local infiltration provides better pain relief after total knee replacement, tonsillectomy, craniotomy, endodontic treatments, and caesarean section.[35-38] No harmful side effects of local dexamethasone use were observed in previous studies during this time. However,

to the extent of our knowledge, scarce data comparing the effects of dexamethasone in wound infiltration as an adjuvant to local anesthetics after lumbar surgery were provided. Thus, this randomized, double-blind clinical trial was conducted to evaluate the effectiveness of adding dexamethasone to ropivacaine in the infiltration of laminectomy and osteosynthesis surgical wounds. Local infiltration of dexamethasone has been revealed to be more effective than its systemic administration.[39-41]

In this study, the use of dexamethasone as an adjuvant was found to delay the use of morphine during the post-surgical period. This is similar to the results found in a recent study conducted in China, which included 80 patients undergoing craniotomy. The study found that the estimated median time of first morphine demand was 24 hours in the RD-group and 8.5 hours in the R-group with p=0.0025.[42] Another study conducted in 2019, including 120 patients undergoing tonsillectomy± adenoidectomy, concluded that the addition of dexamethasone to ropivacaine infiltration provided more efficiency than ropivacaine alone, with a higher analgesic duration and better post-tonsillectomy pain control.[43]

Additionally, our study found that adding dexamethasone to ropivacaine in infiltration of the laminectomy surgical wound reduced the total dose of morphine consumed during the first post-operative 48 hours compared to the R-group, thereby reducing its side effects. Several studies in the literature have shown similar results, including one conducted in Ain Shams University Hospitals in Egypt from October 2018 to February 2019,[44] which evaluated the efficacy of dexamethasone as an adjuvant for bupivacaine in subcutaneous local anesthesia infiltration for skin graft donor sites. The study found that the total morphine consumption was significantly lower in the bupivacaine plus dexamethasone group than in the bupivacaine only group. Another recent study conducted in India in 2021,[45] which included 64 patients undergoing nephrectomy found that dexamethasone plus ropivacaine was more powerful than ropivacaine alone, and the cumulative dose of opioid postoperatively in the R-group was much higher than in the RD-group.

In order to objectively evaluate the clinical effect of drug infiltration, the visual analogue scale (VAS), a one-dimensional measure of pain intensity,[46] was used in our study. The patients were explained how to use it before the study. The current results showed significantly lower scores in the RD-group than the R-group at H4, H6, H12, and H24 postoperatively (P<0.05). However, there was no difference in pain reported between the two groups after 24 hours. A similar result was reported in a recent study published in 2021, which evaluated the efficacy of dexamethasone added to ropivacaine after total knee arthroplasty.[47] The results showed that patients in the RD-group had significantly lower resting VAS scores at 6 and 12 hours after surgery, and lower VAS scores during follow up to 24 hours after surgery. However, results from Rao et al.'s study,[48] in 2020, which aimed to evaluate the analgesic effect of

incision-site infiltration with ropivacaine alone or with adjuvants clonidine or dexamethasone for postoperative pain temporomandibular joint ankylosis surgery, did not show any significant difference in VAS scores at rest and during movement between the three groups. Several side effects may be associated with incision-site infiltration of dexamethasone, such as impaired wound healing,[49] or infections.[49,50] Meanwhile, previous studies have not concluded any complications related to the use of dexamethasone as an adjuvant to local anesthetic in patients undergoing cesarean section, joint replacement surgery, tonsillectomy, abdominal, and lumbar surgery.[35-38] Besides, steroid complications, such as peptic ulcer, wound infection, and impaired wound healing, are generally associated with long-term systemic use.[51,52]

Similarly, in our study, we did not report any side effects of dexamethasone from the first 24 hours postoperatively to the following 3 months. Zhao et al, in their clinical trial in 2021 enrolling patients undergoing supratentorial craniotomy, reported that patients in the RD-group (70%) had excellent wound healing compared to those in the R-group (61%). Additionally, there was a lower wound infection rate in the RD-group (0%) versus the R-group (0.7%, one patient).[31,42,44,47,53-58] Therefore, dexamethasone as an adjuvant to incision-site infiltration is a safe method for the prevention of incision-site pain after spinal surgery.

Furthermore, this present study has demonstrated that incorporating dexamethasone as an adjuvant to local anesthetic in lumbar spine surgery leads to a significant reduction in hospital stay duration, earlier mobilization, and improved rehabilitation. Our findings are consistent with previous studies. For instance, in one study, patients who underwent lumbar discectomy and received bupivacaine and methylprednisolone via wound infiltration reported complete pain relief on the first postoperative day, required less postoperative opioid analgesia, and had significantly shorter hospital stays than the control group who received bupivacaine alone.[59]

Similarly, Rasmussen et al. found that the introduction of steroids via wound infiltration in patients undergoing lumbar discectomy decreased hospitalization duration from 8 to 6 days, with a significant difference (P=0.0001).[60]

Chronic postoperative pain is a debilitating condition that can lead to disability, reduced quality of life, and increased healthcare expenditure.[61] Dexamethasone, through its late effect of inhibiting the proliferation of intercellular proteoglycans and collagen, reduces adhesion and fibrosis formation,[62] and thereby may lower the incidence of chronic pain. In our study, we observed no instances of chronic pain in the RD-group, compared to two patients in the R group, though there was no statistically significant difference. These findings are consistent with previous studies. For instance, a randomized clinical trial,[60] comprising 200 patients who underwent lumbar discectomy aimed to evaluate the efficacy of steroids in

preventing long-term neurological pain after surgery. The study reported that the proportion of patients with neurological impairment was lower in both groups at 2 months post-operative and more so in the RD-group than the R-group (70% vs. 44%, p < 0.0004).

Limitations

There are several limitations in the present study that should be noted. In the first instance, the pandemic had a significant impact, resulting in a reduced number of eligible patients and a smaller sample size of 30 patients in each group.[63] Second, the primary observational measurement relied on the VAS score for postoperative pain, which is inherently subjective and could introduce bias due to individual differences in pain perception. Additionally, the study was conducted at a single center with the same surgical and anesthesia teams, which may limit the generalizability of the findings. As a result, further multi-center studies are necessary to confirm the results and evaluate the efficacy of the proposed intervention in a more diverse patient population.

CONCLUSION

In conclusion, our study demonstrated that the use of dexamethasone in combination with ropivacaine for preemptive incision-site infiltration resulted in a significant reduction of postoperative pain in patients undergoing spinal surgery. Moreover, this approach led to a decrease in the need for opioids, delayed the time of first analgesic demand, and resulted in shorter postoperative hospital stays without an increase in side effects. Therefore, the use of intraoperative dexamethasone with ropivacaine wound infiltration is a safe, simple, and effective method for postoperative pain management. Future multi-center studies should be conducted to further evaluate this approach in a larger patient population.

List of abbreviations

ANOVA: Analysis of variance.
ASA: American Society of Anesthesiologists
BMI : Body mass index
COVID: Corona virus disease.
H: Hour
PACU: Post-anesthesia care unit
PCA: Patient controlled analgesia
PROSPECT: Procedure specific postoperative pain management.
RD-group: Ropivacaine and dexamethasone group
R-group: Ropivacaine group
VAS: Visual analogue scale.
SFAR: French society of anesthesia and resuscitation.
SPSS: Statistical packages for social sciences.

Disclosure

The authors report no conflict of interest in the materials or methods used in this study or the findings specified in this paper

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