Postoperative analgesia after wound infiltration with Dexmedetomidine and Ropivacaine versus Ropivacaine alone for lumbar discectomies: a randomized-controlled trial

Infiltration para-vertébrale au cours de la chirurgie du rachis lombaire : Ropivacaine versus Ropivacaine+Dexmédétomidine, étude randomisée contrôlée

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RÉSUMÉ

Introduction : L'efficacité clinique des anesthésiques locaux (AL) disponibles actuellement sur le marché est limitée par leurs demi-vies relativement courtes. Plusieurs auteurs soulignent le rôle important des α2-agonistes tels que la dexmédétomidine (DEX) dans le contrôle de la douleur post opératoire (DPO) lorsqu' elle est associée aux AL.

Objectif: comparer l'efficacité analgésique de l'utilisation de la ropivacaine seule (R) en infiltration de la plaie chirurgicale après discectomie lombaire versus: ropivacaine+ DEX.

Méthodes : Etude prospective, contrôlée, randomisée, en double-aveugle, Les patients adultes proposés pour chirurgie du rachis lombaire à froid ont été randomisés en deux groupes: groupe (R) reçoit 2mg/kg de ropivacaine: 4.75 mg/ml en infiltration, groupe RD reçoit la même dose de ropivacaine avec 0.5 ug/kg de DEX. L'échelle visuelle analogique (EVA) a été évaluée à h (heure) 0, 2, 6, 12, 18, et 24 ainsi que le temps moyen de la première demande d'analgésie et la dose totale de morphine consommée durant les 24 h post-opératoire (POP).

Résultats : L'EVA a été significativement plus basse (p<.10-3) dans le groupe RD que le groupe R. Le temps médian pour la première demande analgésique était significativement plus bas dans le groupe (R) :8h [6-12] que le groupe RD. La valeur pour la médiane du temps pour le groupe RD: 21 h[18-24]. La dose médiane (intervalle interquartile) de la morphine consommée était de 3 [3-6] mg dans le groupe (R) et 0 [0-2] mg dans le groupe RD. Le temps du premier lever POP était aussi plus court dans le groupe RD (22±03 h) que le groupe R (27±06 h).

Conclusions: L'infiltration de la plaie chirurgicale par l'association DEX et ropivacaine était supérieure pour le contrôle de la DPO que la ropivacaine seule.

Mots-clés

Chirurgie, Déplacement du disque intervertébral, Douleur post-opératoire, Dexmédétomidine, Ropivacaine

SUMMARY

Introduction: Current LA may provide solid analgesic effect however, their analgesic advantages might be limited by their short life. Several reviews highlight the potential role of α2-adrenergic receptors agonists like dexmedetomidine (DEX) for postoperative pain control.

Aim: Compare the analgesic efficacy of the sole LA: ropivacaine (R) with the combination of both: ropivacaine and DEX (RD) for wound infiltration (WI) in lumbar discectomies.

Methods: Prospective, randomized, double-blind, controlled study in nature. Adult patients undergoing elective lumbar discectomies were randomly allocated into two groups: group (R) received 2mg/kg with ropivacaine: 4.75 mg/ml in WI, group RD received the same dose of ropivacaine as the first group adding 0.5 ug/kg of DEX. Visual analog scale (VAS) at 0, 2, 6, 12, 18, and 24 hours (h); time to first rescue analgesia, total post-operative opiate dose were assessed during the first 24 h postoperatively.

Results: VAS values at all time intervals were significantly lower (p< 10-3) in the RD group as compared with the R group. The median time to first rescue analgesia was significantly shorter in the R group 8h [7-12] than RD group 21 h [18-24]. The median (interquartile range) opioid use was 3 [3-6] morphine mg equivalents in the R group and 0 [0-2] morphine mg equivalents in the RD group. The first time to mobilization was significantly shorter in RD group (22±03 h) than R group (27±06 h).

Conclusions: WI with combined ropivacaine and DEX found to be significantly superior for postoperative analgesia compared with ropivacaine alone for lumbar discectomies.

Key-words

Lumbar discectomy, Post-operative pain, Dexmedetomidine, Ropivacaine

INTRODUCTION

Treatment of postoperative pain (POP) is a key element of enhanced recovery after surgery program (1), considered actually as the standard of care and best practice in many surgical specialties. Alleviating POP linked with lumbar disc surgeries is crucial as it can lead to earlier mobilization, decreased side effects from narcotic medications as well as length of stay and improved patient satisfaction (2). Many recent reports stated that the intensity of acute POP is a risk factor for developing chronic postoperative pain (CPOP) which is a poorly recognized potential outcome from surgery (3). Chronic pain, affects the quality of life of patients and increases the risk of long-term analgesic use. It also increases indirect medical costs through job absenteeism and loss of productivity (3). Thus, well managing POP has not only ethical issues but also a pharmacoeconomic impact.

Wound infiltration with local anesthetics (LA) is a widely used technique to optimize POP. Current LA may provide solid analgesic effect by inhibiting nociceptive transmission from peripheral to central neuronal system. However, their analgesic advantages might be limited by their short life. Different adjuvants when added to LA **prolong** POP analgesia (4). Several reviews highlight the potential role of α-2 adrenergic receptors agonists like dexmedetomidine (DEX) for POP pain control (5,6).

The main aim of our study was to compare analgesic efficacy of the sole LA: ropivacaine (R) with the combination of both: ropivacaine and DEX (RD) after wound infiltration in lumbar discectomies. Patients were then followed up over a six-month period to asses neuropathic pain (NP).

METHODS

This prospective randomized study was conducted in the neurosurgical operating room in the military hospital of Tunis between August and December 2018. The local Institutional Review Board of the hospital approved the study protocol (approved number 12/2018). We have followed the CONSORT recommendations for reporting randomized, controlled clinical trials (7).

Patients

Patients aged 18-70 years-old, belonging to American Society of Anesthesiologists' (ASA) physical status 1 and 2, of either sex were recruited if an elective single space lumbar-discectomy was planned. Patients shedulded to redo lumbar discectomy were not eligible for inclusion. Other exclusion criteria included long-term use of analgesic medications (two months for narcotic medication and three months for non-steroid anti-inflammatory drugs, tramadol or anti-epileptic drug as pregabaline…), hemostasis disorders, history of thromboembolic events, altered mental status or serious psychiatric disorders, laminectomy extended to more than one level (not planned before surgery) or a dural breach. Patients were then randomly allocated into two equal groups using computer-generated randomization table (block size six):

-Group (R) received 2mg/kg (IBW: ideal body weight) of wound infiltration with ropivacaine 4.75 mg/ml without exceeding a total volume of 30 ml.

-Group RD received the same dose of ropivacaine as the first group adding 0.5 ug/kg IBW of DEX without exceeding the volume of 30 ml.

Medications were prepared by another anesthesiologist not participating in the study so that neurosurgeon and anesthesiologist who took care of the patient were kept blinded to the study methodology. Injection solutions were prepared following the principles of sterile techniques. To obtain the concentration of 4.75 mg/ml of ropivacaine, 15 ml of a 7.5 mg/ml ropivacaine solution were mixed with an equal volume of 2mg/ml one, to give 30 ml at 4.75 mg/ml. The mixture was injected with the volume required, immediately by neurosurgeon who performed a wound infiltration over the incision line, on the paravertebral muscles, sub-cutaneous and cutaneous tissue, just before closure after discectomy. In the operation theater, electrocardiogram, noninvasive blood pressure and monitor pulse oximeter were connected and baseline readings were obtained from each patient. In each of the two groups, conventional general anesthesia technique was used. All patients were induced with IV propofol 2.5 mg/kg, remifentanil 0.5-1µg/kg, cisatracrium 0.15mg/kg and intubated after three minutes with proper-sized cuffed endotracheal tube in supine position. A single dose of four mg of dexamethasone was given intravenously after the induction of anesthesia. Patients were then turned into prone position with proper care and anesthesia was maintained with a propofol infusion rate of 6 mg/kg/h to 12 mg/kg/h and remifentanil infusion rate of 0.05-2 gamma/kg/**min**. Flow rates for drug syringe pumps were adjusted

when mean arterial pressure (MAP) or heart rate (HR) rose or dropped 20% above baseline values. Just before closure after discectomy, surgeon infiltrated the prepared study drug as described above. Furthermore, 30 minutes before the end of surgery, patients were given multimodal analgesia based on 0.1mg/kg of morphine, 15mg/kg of paracetamol and 20 mg of nefopam. The time from onset to the end of the surgical procedure was noted as the duration of surgery. Blood loss volume was also noted. At the end of surgery, after turning all the patients supine, patients were extubated successfully on the table. Once completely awake and responded to verbal commands, they were shifted to postoperative wards where pain at the incision site was assessed using visual analogue scale (VAS) by another blinded anesthesiologist from all patients at 0, 2, 6, 12, 18, and 24 h. During a preoperative visit, the patients were introduced to the concept of VAS, with a 10-cm vertical score ranged from 0 = no pain to 10 = worst pain imaginable. VAS score > 3 was taken to indicate significant pain and used as a cut off point for rescue analgesia with paracetamol, tramadol or ketoprofen according to patient-conditions and to what he received in the operating room. If all these **medications** failed to alleviate pain, morphine titration was used. Primary outcome was total postoperative opiate consumption during the first 24 h. Secondary outcomes were time to first rescue analgesia, VAS and hemodynamic data (MAP and HR) at 0, 2, 6, 12, 18, and 24 h, narcotic and DEX side effects, sedation score using Ramsay sedation scale (RSS during the first two postoperative hours), time to first lift. Thromboembolic events and chronic neuropathic pain (NP) were assessed during a six-month follow-up.

Statistical analysis

Data were analyzed statistically using software SPSS (Statistical Package for the Social Science) version 20.0.0 (SPSS Inc., Chicago, IL). Sample size was calculated based on results of a previous study carried out (8). At an error of 0.05 and power of 80%, taking minimum detectable diference in morphine use to be 20% and SD of 5, sample size was calculated to be 25 subjects in each group. For study purpose, 30 subjects were taken in each of the 2 groups. The normality of data established using Shapiro-Wilk test. Data were reported as mean and standard deviation for parametric data or median with a 25% and a 75% range for non-parametric data. Categorical data were presented as numbers and percentages. Comparisons of means were conducted using analysis of variance. The chi-squared test was used to analyze categorical variables. A two-sided $p < 0.05$ was considered statistically significant.

RESULTS

We had initially recruited 73 patients. Ten patients were secondarily excluded for the following reasons: performing more than one level discectomy, four dural breach and two wound infiltration intraoperatively with dexamethasone for fibrosis in the surgical site (figure 1).

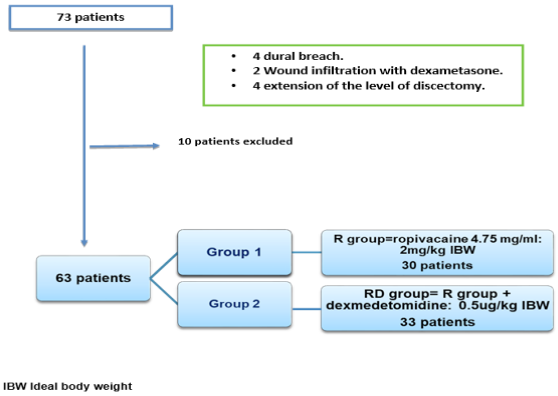
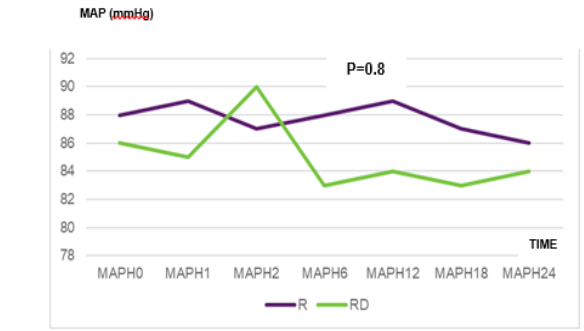


Figure 1 ; Flowchart of recruited patients

Our results showed that the two groups of patients were comparable for all demographic and clinical data (Table 1). VAS values at all time intervals were significantly lower ($p<.0001$) in the RD group as compared with the R group (figure2). The median time to first rescue analgesia was significantly shorter in the R group 8 h [7-12] than RD group 21 h [18-24] ($p<.0001$). Median (interquartile range) opioid use was 3 [3-6] morphine mg equivalents in the R group and 0 [0-2] morphine mg equivalents in the RD group during the first 24 h. In-parallel, HR was statistically higher in R group (ANOVA $p =0.002$) (Figure 3). However, there was no statistically significant difference in MAP between the two groups (ANOVA $p =0.8$) (Figure 4). The first time to mobilization was significantly shorter in RD group (22±03 h) vs R group (27±06 h). No statistically significant side effects due to morphine or DEX use could be discerned among the two groups in the postoperative period: (nausea, vomiting, constipation, desaturation or sedation as shown by RSS in the first two hours in postoperative period (figure 5). Five patients experienced acute urinary retention (three in R group and two in RD group) which resolved within 24 h.

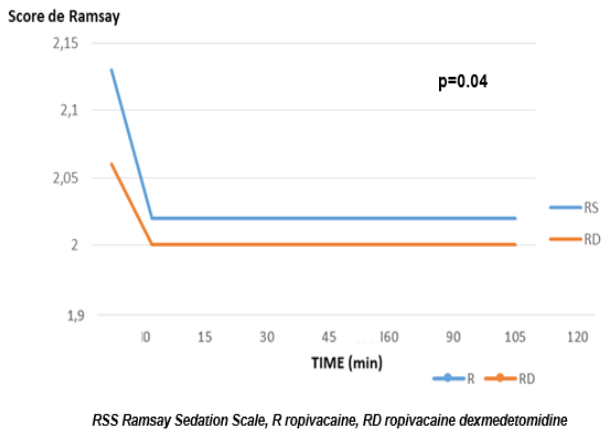
R ropivacaine, RD ropivacaine dexmedetomidine, ppm pulse per minute, H hour, HR heart rate

Figure 2. Evolution of postoperative VAS during the first 24 hours



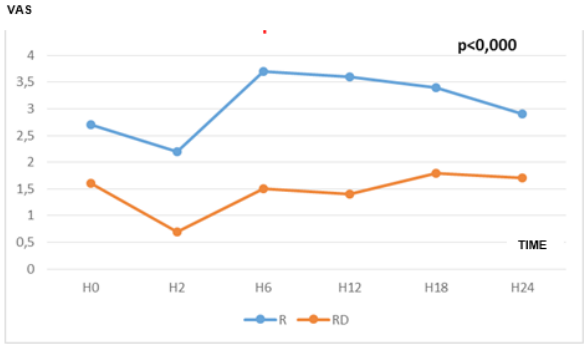
R ropivacaine, RD ropivacaine dexmedetomidine, p statistical significance, H hour, MAP mean arterial pressure

Figure 3.Heart rate changes between groups during the first 24 hours



RSS Ramsay Sedation Scale, R ropivacaine, RD ropivacaine dexmedetomidine

Figure 4. Evolution of mean arterial pressure during the first 24 hours post surgery



VAS Visual analogue scale, R ropivacaine, RD ropivacaine dexmedetomidine, H hour

Figure 5. RAMSAY score evolution during the first 24 hours

Table 1 : Demographic and clinical characteristics of the study population

	R group	RD group	p
Age (years)	48.13±12.6	44.15±12.8	0.21
Sex-ratio	18/12	19/14	0.52
ASA I	56.6	60.6	0.47
II	43.4	39.4	
Weight (kg)	76.6±11.1	77.76±10.9	0.67
Height (cm)	173.6±19.7	171.61±13.8	0.6
Smoking (PY)	10.7±3.4	11.3±2.8	0.63
Alcohol consumption (%)	6.66	24.2	0.57
Preoperative VAS	5.23±1.4	4.71±1.7	0.28
Preoperative pain	3[2-15]	4[2-8]	0.89
duration (months)			
Total of volume	26.7±3.3	27.2±2.8	0.52
infiltration (ml)			
Duration of operation (min)	122.5±52.4	117.88±35.5	0.68
Intra-operative blood loss (ml)	234±144.49	203.33±110.21	0.34

R ropivacaine, RD ropivacaine dexmedetomidine, ASA American Society of anesthesiology, VAS visual analogue scale, PY paquet year, ml milliliter, min minute

During the follow-up period, we did not register any thromboembolic event. We found only five patients off 66 with persistent NP at three-month follow up. These patients were followed up by telephone at six months. Only one patient still suffering from NP and local infiltration with LA was planned. Of the remaining patients, one was operated a second time for recurrent disc herniation and three relieved their pain with medical treatment (Table 2).

Table 2. Characteristics of patients with chronic neuropathic pain at three and six-month follow-up

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Group	R	R	RD	R	R
Age (YO)	54	24	47	50	31
Sex	M	M	F	F	F
IBW (kg/m²)	26	23	24	27	36
Medical History	Diabetes mellitus, hypothyroidism	-	-	-	-
Tobacco (PY)	10	3	0	0	0
Alcohol	NO	YES	NO	NO	NO
Preoperative VAS score	6	4	5	6	6
Preoperative pain duration (months)	2	5	12	3	2
Preoperative NP	YES	YES	YES	YES	YES
Preoperative DN4	5	4	6	4	4
Per-operative bleeding (ml)	350	250	300	180	300
Length of surgery (min)	150	60	95	60	120
DN4 at 03 months	6	5	4	5	4
DN4 at 06 months	1	1	5	2	0
Repeated MRI at 03 months	Post- operative epidural fibrosis hernia recurrence	-	Post-operative epidural fibrosis	-	-
Management of NP	Second **discectomy** 05 months later/ laminectomy L4	Medical TTT	Dexamethasone infiltration+ medical TTT	Medical TTT	Medical TTT
Outcome	Favorable	Favorable	**Persistent** NP	Favorable	Favorable

R: ropivacaine group, RD: ropivacaine dexmedetomidine group, YO: years old, M: male, F: female, PY: packs per year, VAS visual analogue scale, MRI magnetic resonance imaging, NP neuropathic pain, L4 fourth lumbar vertebrae, TTT: treatment

DISCUSSION

Infiltration with LA around the surgical wound is an effective analgesic technique, which could decrease postoperative wound pain and analgesic usage (9). Hopf et al (10) demonstrated that POP rises both tissue inflammation and plasma catecholamine level causing impaired wound perfusion and oxygenation. Wound infiltrations with LA agents along could then provide effective pain control and promotes faster wound healing.

Our results showed that wound infiltration with either R or RD was associated with a reduced POP morphine consumption with a more significantly result with RD group. Before implementation of postoperative wound infiltration with LA, patients who underwent lumbar discectomies in our neurosurgery department needed frequently morphine intravenous titration (non-published data). Low doses of morphine consumption in our study may be explained by the multimodal analgesic POP regimens. Compared with R group, DEX intervention was also associated with a significantly reduced pain score during the first 24 h after surgery, improved duration of analgesic effect and shorter time to first lift. LA infiltration after lumbar discectomies is becoming a promising tool to manage POP as it is easy to perform, cost-effectiveness with fewer adverse effects (2). The beneficial effects of infiltrating incision line with various LA agents have been documented in numerous studies. In line with our results, Mitra et al (11) concluded that wound infiltration with combined ropivacaine and DEX found to be significantly superior for postoperative analgesia compared with either combined ropivacaine and tramadol or ropivacaine alone for lumbar discectomies. The authors used lower volume with nearly the same concentration of ropivacaine (20 ml of ropivacaine 5%) compared with our study. There is a debate in the literature regarding the appropriate volume and concentration of LA to use.

Ilfeld et al (12) found that the total dose of LA was the main factor affecting the clinical results in hip arthroplasty among their study population. On the other hand, Mosaffa et al (13), reported that the volume of the injected anesthetic accelerated the onset of sensory and motor infraclavicular block without affecting the rate of success in their patients. In our study, using higher volume for wound infiltration provided 3.5 hours delay in ropivacaine group and 5.5 hours delay in RD group in median time to first rescue analgesia, when comparing our results with those of Mitra et al. Furthermore, in this current trial, 0.5mg/kg dose of DEX was used as an adjuvant based on past studies (14). There are very few studies regarding the use of DEX as an adjuvant to LA agents in lumbar paravertebral wound infiltration (11) and almost no pharmacokinetic studies.

Many other reports highlighted the efficacy of adding DEX to ropivacaine in reducing POP in other surgeries such as: incision infiltration after laparoscopic cholecystectomy (15), lower segment cesarean section (16), open gastrectomy (17)…

DEX is a highly selective and strong α2-adrenoceptor agonist with α2:α1 binding ratio of 1620:1 with known sedative, antihypertensive, anxiolytic, and analgesic properties (18). α2-agonists exert their analgesic action on numerous sites like brain, spinal cord, and peripheral tissue (19). It has gained widespread clinical applications as an adjuvant to LA for peripheral regional anesthetic techniques (20–22). However, there are few clinical studies regarding DEX added to LA for wound infiltration. The exact mechanism of action of DEX on peripheral nerve is still debatable but three possible theories have been advanced. First, it may be due to direct inhibition of impulse firing in primary afferents C fibers leading to a possible local anesthetic like action on the peripheral nerve (23). Second, local vasoconstriction due to α2-agonist mediated action on postsynaptic adrenergic receptors may explain decreased absorption of the LA solution from the infiltration site (24,25). Third, DEX increases the action of LA solution by acting on peripheral α2- adrenoceptors (26).

The Second part of this study focused on estimating the prevalence of persistent or recurrent NP using DN4 questionnaire, during a six-month follow-up period. The prevalence of patients with chronic radicular NP who had previous spinal surgery (so called failed back surgery syndrome) is not well designed and probably comparable to other pain associated diseases such as chronic arthritis (27). The low incidence of post-surgical NP in our series at follow-up is probably due to the minimally invasive surgical technique as well as the multimodal analgesic approach. Some clinical trials have demonstrated that the use of multimodal regimens to manage pain during surgery is associated with a decreased incidence of CPOP (28–30). A recent Cochrane systematic review assessing LA at the time of surgery to prevent longer-term persistent pain after surgery demonstrated low to moderate-quality of evidence to reduce the risk of developping POP depending on the type of surgery (31).It is worthy to note that their conclusions were weakned by the low quality of evidence of the included studies. However, there is more and more supporting literature highlighting the role of DEX in controlling chronic NP. This is due to the anti-inflammatory action of DEX (32) as well as down regulation of satellite glial cells activation, nerve growth factor expression and sympathetic sprouting (33). The sample size of our study and absence of placebo group can't draw any conclusion about the effect of LA or DEX in preventing chronic NP.

The present study has got some limitations. First, it did not include an untreated local infiltration group for ethical reason. Second, it was carried out only on one-lumbar discectomy level as pain perception will differ depending on the number of levels of spine involved. Third, we did not measure plasma concentrations of DEX which could help to confirm whether its action and clinical findings were related to systemic absorption or local effects. Furthermore, we did not measure plasma concentrations of ropivacaine as pharmacokinetic data are lacking for intramuscular paravertebral injection. Finally, the optimal dose and methods of DEX for paravertebral wound infiltration surgery remained elusive and required more clinical and pharmacokinetic studies.

CONCLUSION

We concluded that wound edges infiltration with combined ropivacaine and DEX found to be significantly superior for postoperative analgesia compared with ropivacaine alone for lumbar discectomies. Both groups of patients had low prevalence of NP during follow-up period of six months. Pharmacoeconomic studies are warranted to justify the use of expensive adjuvant as DEX for pain relief in lumbar spine surgery.

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