The Effect of Intraoperative Infusion of Dexmedetomidine on the Quality of Recovery After Major Spinal Surgery

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Background: Surgery induces a variety of metabolic, endocrine, and immune changes collectively known as the "stress response," which may often lead to prolonged postoperative convalescence. Anesthetic management may modulate this physiological response, thus affecting the postoperative course. We hypothesized that the intraoperative administration of dexmedetomidine (DEX), a sympatholytic agent, would reduce the stress response and improve the quality of recovery in patients undergoing major surgery.

Methods: We conducted a prospective randomized double-blinded study of 54 patients undergoing multilevel spinal fusion. Anesthesia was maintained using either propofol/fentanyl/dexmedetomidine (PFD) or propofol/fentanyl/placebo-saline (PFS). The quality of recovery (a primary endpoint) was assessed using a 40-item quality of recovery questionnaire and a 9-question Fatigue Severity Scores. The tests were carried out preoperatively on postoperative days (POD) 1, 2, 3, and 30. Blood samples were collected at baseline, in the postanesthesia care unit, and at POD 1 and were analyzed for levels of cortisol, C-reactive proteins (CRP), and cytokines interleukin (IL)-1α, IL-1β, IL-1ra, IL-2, IL-6, IL-8, IL-10, and tumor necrosis factor-α. Data were analyzed using SPSS software (version 18) using a multivariate and mixed model approach to test for the effect of surgery and drug group. Pairwise comparisons were assessed by means of the *t* test or rank tests after correcting for multiple comparisons.

Results: The global 40-item quality of recovery questionnaire scores showed a significant effect of time ($F_{4,114} = 22.63$, $P < 0.001$) and drug ($F_{1,51} = 4.368$, $P = 0.042$), with average scores decreasing to lower values on POD 1 (163.63 ± 2.47) and POD 2 (170.94 ± 2.38) compared with baseline (180.56 ± 1.588, mean ± SE, 2-tailed *t* tests, $P < 0.001$). By POD 3, scores were significantly lower (−13.74 point difference, $P = 0.005$) in the PFS group (169.3 ± 3.87) than in the PFD group (183.04 ± 2.76). All patients reported significantly higher levels of fatigue postoperatively, but intergroup difference in Fatigue Severity Scores was detected on POD 3 only, with scores in the PFS group higher than in the PFD group (50.0 ± 4.0 vs. 36.3 ± 4.9, $P = 0.035$). In both groups, plasma cortisol levels were highest in the postanesthesia care unit, whereas CRP levels were elevated on POD 1. DEX significantly reduced the levels of cortisol, but not those of CRP. Levels of cytokines IL-6, IL-8, and IL-10 were significantly higher immediately after surgery and at POD 1. Plasma levels of other cytokines were not affected by surgery. DEX delayed postoperative rise in IL-10 but not in IL-6 or IL-8.

Conclusions: DEX infusion during multilevel spinal fusions moderately improved the quality of recovery and possibly reduced fatigue in the early postoperative period. Moreover, it reduced plasma levels of cortisol and IL-10 in comparison with the control group. Our sample size was not sufficient to detect differences either in the incidence of complications or in clinically relevant outcomes.

Key Words: postoperative recovery, dexmedetomidine, spine surgery, cytokines, cortisol, C-reactive protein

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The association between surgery-induced neuroendocrine and inflammatory responses, anesthetic management, and both short-term and long-term outcomes is being increasingly recognized by the anesthesia community. Surgical injury to tissue causes a variety of profound physiological reactions that are essential for the restoration of an organism's homeostasis. The response involves a surge of stress hormones [ie, C-reactive protein (CRP), cortisol, and catecholamines], activation of the complement system, migration of leukocytes to the site of injury, the release of cytokines (eg, interleukins and tumor necrosis factor), and other cellular products (ie, superoxide radicals, proteases, and growth factors).[1–2] An appropriate inflammatory cascade is essential for tissue reconstitution and infection control. Because of the

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physiological reserve of biological systems, the associated impairment of multiple organ function is generally mild. However, a systemic inflammatory response may lead to postoperative complications among the elderly, in neonates, and in patients with significant comorbidity.[3–5] In addition, mediators of inflammation may induce fatigue and prolong convalescence in otherwise healthy patients. Thus, modulation of the immune response may reduce the incidence of postoperative complications and improve recovery.

Anesthetic management may affect both immunostimulatory and immunosuppressive mechanisms directly by modulating immune cell function or indirectly by attenuating the stress response. Thus, the choice of the anesthetic technique may affect clinical outcomes by perturbing the balance between proinflammatory and anti-inflammatory responses. It is well documented that dexmedetomidine (DEX) inhibits the neuroendocrine and inflammatory response in various experimental and clinical settings. Recent evidence suggests that DEX decreases the production of inflammatory cytokines while lowering intra-abdominal pressure in critically ill patients with sepsis.[6] Animal studies also indicate that DEX attenuates the increase in plasma cytokine levels after endotoxin injection and markedly reduces the mortality rate of infected animals.[7] These results suggest a role for DEX in preventing unwanted stress responses, mitigating postsurgical convalescence, and possibly of reducing the rate of complications during the convalescence period. However, so far, there have been no studies that have attempted to correlate DEX-produced attenuation of stress and the quality of recovery from surgery.

The aim of the present study was to examine whether changes in the concentrations of stress hormones and inflammatory mediators correlate with meaningful clinical outcomes. We measured circulating levels of cortisol, CRP, and cytokines [interleukin (IL)-1α, IL-1β, IL-1ra, IL-2, IL-6, IL-8, IL-10, IL-12, and tumor necrosis factor (TNF)-α] in patients undergoing multilevel spinal fusion. In addition, patients were assessed for the quality of recovery, level of fatigue, and cognitive function. A 40-item quality of recovery questionnaire (QoR40), a 9-question Fatigue Severity Scores (FSS), mini-mental examination (MMSE), and digital span forward (DSF) and backward (DSB) were administered at baseline and on postoperative days (POD) 1, 2, 3, and 30 (QoR40 and FSS only). Patients received either propofol/fentanyl/dexmedetomidine (PFD) or propofol/fentanyl/placebo-saline (PFS). We hypothesized that the addition of DEX would reduce levels of stress markers associated with sickness behavior, thus improving the quality of recovery.

METHODS

After obtaining approval from the Institutional Review Board at the New York University School of Medicine and written informed consent from patients, we enrolled 66 adult patients scheduled for elective multilevel lumbar fusion surgery. Exclusion criteria included cognitive impairment, chronic use of antipsychotic medications, treatment using α-2 agonists or antagonists within 2 weeks of study entry, chronic use of anti-inflammatory drugs (ie, steroids, NSAIDs, etc.), or a history of kidney or liver disease. Patients were randomly assigned to 1 of 2 treatment groups. Randomization was based on computer-generated random-block codes maintained in sequentially numbered envelopes. Randomization was stratified by site. Pharmacy-prepared 60-mL syringes containing either DEX (0.4 mcg/mL) or placebo were given to responsible anesthesiologists. Neither anesthesiologists nor patients were cognizant of the treatment groups (double-blind design). The investigator who was unaware of the treatment groups and was not involved in patients' intraoperative care performed postoperative evaluations.

Surgery and Anesthesia

General anesthesia was induced using propofol (1.5 to 2 mg/kg) and fentanyl (2 to 5 mcg/kg). Rocuronium (0.6 mg/kg) was used to facilitate endotracheal intubation. Patients were ventilated using an oxygen-air mixture ($FiO_2 = 0.4$) with $PetCO_2$ stabilized at 30 to 35 mm Hg. Infusion of the study drug began after placement of the intravenous line, was maintained throughout the procedure, and stopped approximately 20 minutes before the completion of surgery. The infusion rate was fixed at 0.5 mcg/kg/h of DEX (or matching placebo). Paralyzing agents were not used during the operation to facilitate the intraoperative monitoring of motor-evoked potentials. The infusion rate of propofol was adjusted to maintain the depth of anesthesia at a bispectral index level of 45 to 50. Every patient had an arterial line. Phenylephrine and ephedrine (rather than the titration of the anesthetics) were used as needed to maintain mean a arterial pressure between 70 and 90 mm Hg. All patients received ondansetron 4 mg before the completion of surgery. Patients were awakened and extubated in the operating room and transferred to the postanesthesia care unit (PACU) upon following simple commands. In the PACU, all subjects received rescue opioids as indicated by a Numeric Pain Rating Scale score >2 or on the subjects' own request.

Data Collection and Blood Sampling

Blood samples for the analyses of cortisol, CRP, and cytokines were collected before induction of general anesthesia and before infusion of any fluids, in the PACU and on POD 1. Samples were centrifuged within 30 minutes of collection, and plasma was stored at $-70^{\circ}C$ until analysis. Analyses for serum levels of CRP and cortisol were performed using the VITROS 5600 analyzer (Johnson and Johnson, Rochester, NY) at the New York University Langone Medical Center Clinical Laboratories. For CRP measurements, an enzymatic heterogenous sandwich immunoassay is used. A derivative of phosphorylcholine covalently bound to polystyrene polymer beads captures CRP in serum samples. The instrument determines the concentration of CRP by measuring the signal generated by a monoclonal anti-CRP antibody conjugated to horseradish peroxidase (HRP). For cortisol measurements, a competitive

immunoassay is used. An HRP-labeled cortisol conjugate competes with serum cortisol for binding sites on sheep anticortisol antibody. A luminescent reaction is used to measure the bound HRP conjugate, which is indirectly proportional to serum cortisol levels. The sensitivity of the assay for cortisol and CRP was 0.2 mcg/dL and 0.3 mg/L, respectively. Luminex multiplexed bead-based immunoassays for inflammatory mediators were used for analysis of plasma cytokines. Multianalyte profiling was performed on the Luminex-200 system and the XMap Platform (Luminex Corporation). Calibration microspheres for classification, reporter readings, and analysis of sheath fluid were purchased from the Luminex Corporation. Acquired fluorescence data were analyzed using Beadview software. All analyses were performed according to the manufacturers' protocols. The lower limit for all cytokine detection was 1 pg/mL. Lower limits of detection for specific protein standards were obtained on the basis of software extrapolation of diluted standards.

Neurobehavioral Assessments

QoR40 was used to quantify the quality of recovery.[8–9] Five aspects (dimensions) of recovery are commonly measured by these metrics: emotional state (n = 9 items), physical comfort (n = 12), psychological support (n = 7), physical independence (n = 5), and pain (n = 7). The impact of fatigue on recovery was assessed using the 9-item FSS scale, which is one of the most commonly used means of measuring fatigue.[10,11] Five of those FSS items were modified to reflect the perioperative environment (see Appendix 1). A low FSS value (eg, 1) indicates strong disagreement with the statement, whereas a high value (eg, 9) indicates strong agreement. In addition, the MMSE and DSF/DSB were used to assess recovery of cognitive function. Pain intensity was measured using a 10-point numeric digital scale. Subjects were asked to participate in neurobehavioral testing only if they reported a pain level < 2.

A QoR40 questionnaire, FSS assessment, MMSE, DSF, and DSB were administered on POD 1, 2, 3, and 30 (QoR40 and FSS only). The neurobehavioral tests were administered only if patients reported a pain level < 2 on the numerical pain analog scale. All assessments were conducted during the day, generally in the morning.

Statistical Analysis

The QoR40 score on POD 3 was our primary outcome as suggested by Leslie et al.[12] These authors reported QoR scores 166 on day 0 and 175 on day 90 with SD varying from 15 on day 1 to 20 on day 90 in patients who underwent spinal surgery. Myles and Wengritzky[13] recently demonstrated that patients with severe nausea and vomiting postoperatively had a 12-U lower score compared with those without nausea and vomiting—a clinically meaningful outcome. An SD of 17 and a sample size of 27 subjects per group would allow for detecting a 13-U difference in QoR40 scores assuming a 2-sided test with $\alpha = 0.05$ and power of 80%.

Continuous data were tested for normality using the Shapiro-Wilk tests for equality of distribution functions and were reported as mean ± SD. Two-tailed t tests were used to compare equality of baseline characteristics and clinical data. Categorical parameters were compared using the χ^2 test or the Fisher exact test as appropriate. Because only few patients required vasoactive drugs intraoperatively, and because doses of those drugs varied, the data are presented as numbers and proportions but not analyzed.

Mixed model and multivariate analyses were used to examine the response to surgery and drug group of the QoR40, FSS, and MMSE measures, as well as the response of CRP and cortisol to surgery. We could not use a repeated-measures univariate analysis of variance because of the inability to satisfy sphericity assumptions. The analysis considered 2 issues: (1) whether there was a response to surgery (visit); and (2) whether there was a differential response to study drug (randomization). The cofactor "sex" was not significant in the model and was dropped. In addition, we performed contrast analysis of pairwise comparisons of baseline values versus postsurgical time frames of interest (Sidak multiple comparison correction by SPSS). To be responsive to potential deviations from normality, significant comparisons were confirmed by means of pairwise rank tests, especially when analyzing CRP, cortisol, and cytokine levels. Cytokine levels were first log transformed ($\log(1 + x)$), where x was either the actual value (pg/mL) or the minimum value (when measurement generated undetectable levels). The concentrations reported in Table 2 are untransformed values.

We tested our major conclusions using a bootstrap technique (resampling), as this technique is most robust in terms of data assumptions as suggested by Leslie et al[12] and Genser et al.[14] The bootstrap tests included: (1) comparison of drug effects on cortisol measured in the PACU; (2) comparison of drug effect at POD 3 for QoR40 total; and (3) comparison of all subjects at POD 1 versus baseline for QoR40 total (response to surgery). To perform a "robust estimation," we calculated the mean differences and 95% confidence intervals (percentile method) of 1000 resampled groups (n = 28 subjects per group). In addition, we tested for the effect of sex by resampling from our actual groups to generate groups with balanced sex populations (n = 14), which were then similarly analyzed.

RESULTS

A total of 66 patients were recruited. However, 12 patients were excluded from the final analysis because of surgery cancellation (1), unexpected intraoperative complications requiring mechanical ventilation postoperatively (1), missing neurocognitive assessments (2), missing blood collection time points (6), and early withdrawal from the study (1); 1 patient in the PFD group had a postoperative MI and was excluded from the analysis. Thus, 28 patients in the PFS group and 26 patients in the PFD

group completed the study. Patients' characteristics, except male-to-female ratio, were not different between the groups (Table 1). Similarly, there were no significant differences between groups in any perioperative variables. Somewhat surprisingly, the infusion of DEX did not significantly reduce the requirements for either fentanyl (524.1 ± 358.2 vs. 445.2 ± 230.7 mcg, $P = 0.344$) or propofol (2153.7 ± 1258.6 vs. 1545.6 ± 554.6 mg, $P = 0.061$). An equal number of patients in each group required phenylephrine and/or ephedrine treatment (Table 1). The results could not be meaningfully analyzed because of the small number of entries. All 54 patients remained hemodynamically stable perioperatively, and there were no reports of complications related to administration of anesthesia.

TABLE 1. Baseline Characteristics and Perioperative Parameters

	PFS	PFD	*P* (2-tailed)
Age	57.0 (11.1)	55.3 (12.3)	0.588
BMI	29.0 (5.32)	27.9 (3.9)	0.424
Sex (F/M)	13/15	5/21	0.046
ASA status (1/2/3)	0/22/6	1/19/6	0.564
DM, n(%)	5	5	0.900
CAD	4	2	0.441
HTN	10	10	0.835
COPD/asthma	6	1	0.055
Thyroid disease	5	1	0.102
Medications			
β-blockers	2	4	0.336
Ca channel blockers	2	1	0.597
ACEI/ARB	7	6	0.509
Diuretics	3	2	0.569
Duration of surgery	227.3 (93.4)	230.6 (84.7)	0.892
Duration of anesthesia	295.9 (102.2)	304.0 (85.9)	0.755
Crystalloids	2628.6 (1400.8)	2046.2 (741.1)	0.064
Anesthetics			
Fentanyl	524.1 (358.2)	445.2 (230.7)	0.344
Propofol	2153.7 (1258.6)	1545.6 (554.5)	0.061
Dexmedetomidine	None admin	152.92 (58.7)	n = 0.26
Vasoactive drugs	n(%), [mean admin dose]*	n(%), [mean admin dose]	—
Ephedrine	5 (18), [26.0]	5 (18), [19.0]	—
Phenylephrine	1 (3.7), [300.0]	1 (3.7), [300.0]	—
Labetalol	5 (18), [28.0]	None admin	—
Hydralazine	2 (7.4), [10.0]	3 (11.1), [9.3]	—
Metoprolol	2 (7.4) [5.0]	None admin.	—
Glycopyrrolate	4 (15.0) [0.5]	1 (3.7) [0.8]	—
PACU stay (min)	246.2 (150.2)	203.3 (120.8)	0.255
Postoperative nausea	7.1%	11.5%	0.218
Hospital stay (h)	133.5 (104.0)	103.9 (42.1)	0.182

Values are mean + SD.

*For the vasoactive drugs, in which not all of subjects who received the dose, the table gives an n (the no. patients receiving a dose), a % (the percentage of the patients that received a dose), and a mean administered dose (the mean value of the administered doses); patients who did not receive a drug were not included in the calculation of the mean.

ACEI/ARB indicates angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; ASA, American Society of Anesthesiologists; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HTN, hypertension; PACU, postanesthesia care unit; PFD, propofol/fentanyl/dexmedetomidine; PFS, propofol/fentanyl/placebo-saline.

Quality of Recovery

The global QoR40 scores are plotted in Figure 1. Linear mixed model analysis of variance revealed a significant effect of time ($F_{4,104} = 22.63$, $P < 0.001$) and drug group ($F_{1,51} = 4.368$, $P = 0.042$). There was no difference in baseline (BSL) scores. Scores were significantly lower compared with BSL on POD 1 and POD 2 for both groups combined (−18.78, $P < 0.001$; −9.61, $P < 0.001$). QoR40 values returned to BSL on POD 3 (−4.389 difference, $P = 0.229$), continuing to show no difference for POD 30 (3.056 difference, $P = 0.171$). Although QoR40 scores were higher for patients in the PFD group at all time points, these scores were significantly lower in the PFS group by pairwise comparison only on POD 3 (−13.74, $P = 0.005$).

Global QoR40 scores are composed of scores from 5 individual domains, which we also analyzed separately. Analyzing the data using repeated mixed model analysis, we found the significance for study drug in only 1 of the domains, "comfort" ($F_{1,52} = 4.317$; $P = 0.044$; difference = −3.11), although all had a significant response to time ($F_{4,104} > 5.3$, $P < 0.001$). All domains but "pain" displayed a significant change between BSL and POD 1: "comfort" (difference, −5.70; $P < 0.001$); "emotion" (difference, −3.944; $P < 0.001$); "physical independence" (difference, −5.481; $P < 0.001$); and "patient support" (difference, −2.167; $P < 0.001$). Further, "comfort," "emotion," and "physical independence" had scores that were still depressed compared with BSL at POD 2 (−2.63, $P = 0.038$; −3.074, $P = 0.015$; −2.796, $P > 0.001$, respectively). The temporal profiles of "comfort," "emotion," and "physical independence" were all very similar to that of global QoR40—an immediate drop between BSL and POD 1, followed by a slow recovery toward BSL at POD 2 and 3, eventually reaching BSL values at POD 30.

Examining the study drug using pairwise comparisons (PFS vs. PFD), we found the significance for "comfort" at POD 2 (visit 3; 49.26 ± 1.25 vs. 52.74 ± 1.23;

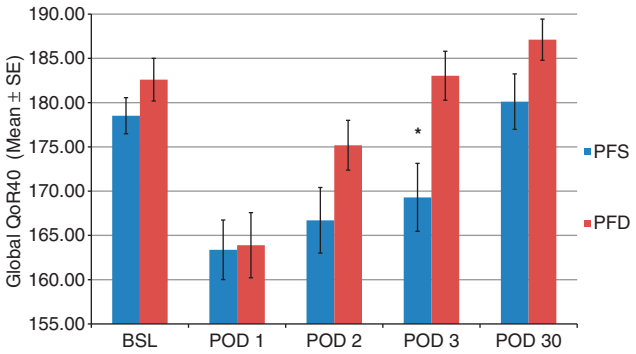

FIGURE 1. Changes in global 40-item quality of recovery questionnaire (QoR40) scores over time. Scores showed a significant effect of time ($P < 0.001$) and drug ($P = 0.042$). Scores were significantly lower in the propofol/fentanyl/placebo-saline (PFS) group than in the propofol/fentanyl/dexmedetomidine (PFD) group on postoperative day (POD) 3 ($P = 0.005$).

$P = 0.032$) and POD 3 (50.19 ± 1.39 vs. 54.67 ± 1.36, $P = 0.005$) and for "patient support" at POD 2 (31.59 ± 1.04 vs. 33.56 ± 0.74, $P = 0.032$) and POD 3 (31.41 ± 0.94 vs. 34.00 ± 0.59, $P = 0.008$).

Assessment of Fatigue

Baseline FSS scores did not differ between the drug groups ($P = 0.291$; Fig. 2). Patients reported significantly higher levels of fatigue postoperatively (POD 1 through POD 3) compared with BSL (BSL-POD 1 = −20.94; BSL-POD 2 = −19.76; BSL-POD 3 = −18.17; $P < 0.001$). By POD 30, the difference was less (−11.46) and no longer significant ($P = 0.058$). Patients in the PFD group had numerically lower scores at every postsurgical evaluation and were significantly lower on POD 3 by pairwise comparison (PFD-PFS on POD 2 = −13.7, $P = 0.035$). This was confirmed by global assessments indicating a significant effect of time ($F_{4,104} = 10.61$; $P < 0.001$) but not of drug group.

Assessment of Cognitive Recovery

MMSE was measured only during hospitalization. It dropped significantly from BSL to POD 1 (−1.33, $P = 0.034$), returning to near BSL values on POD 2 (−0.17 from BSL, $P = 0.99$) and POD 3 (−0.09 from BSL, $P = 0.99$). POD 1 and POD 3 differed by 1.44 U ($P = 0.02$); hence, POD 1 was clearly different compared with both BSL and POD 3. On POD 3, there was a significant difference by study group (28.0 vs. 29.3; $P = 0.011$).

Analysis of DSF and DSB showed no significance by time or drug group or by pairwise comparisons by drug group for a specific time. There were no clear and significant trends as with the previous metrics. However, both DSF and DSB showed a significant drop between BSL and POD 1 examining only PFS subjects. Thus, DSF reduced from 8.56 ± 0.40 to 7.67 ± 0.37, and DSB reduced from 5.26 ± 0.43 to 4.37 ± 0.37 for these patients ($P < 0.05$).

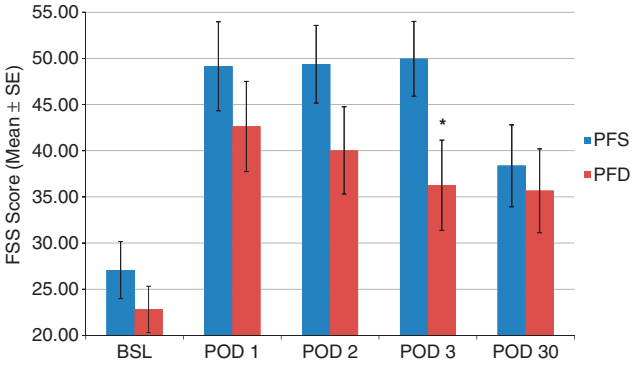

FIGURE 2. Changes in Fatigue Severity scores (FSS) over time. The score showed a significant effect of time (surgery) ($P < 0.001$). Patients in the propofol/fentanyl/dexmedetomidine (PFD) group had numerically lower scores at every postsurgical evaluation and were significantly lower on POD 3 by pairwise comparison [PFD-propofol/fentanyl/placebo-saline (PFS) on postoperative day (POD) 2 = −13.7, $P = 0.035$].

Stress Response

Both cortisol and CRP plasma concentrations increased after surgery. Cortisol levels (baseline 9.76 ± 0825 mcg/dL, mean ± SE) were significantly higher in the PACU for the PFS group than in the PFD cohort (15.25 ± 1.99 vs. 9.86 ± 2.15 mcg/dL, $P = 0.031$, t test). By POD 1, average cortisol levels had returned to slightly above BSL values (11.63 ± 1.18 mcg/dL) and drug group differences were absent (Fig. 3A). A rise in CRP levels was slowest and without statistically significant differences between groups (Fig. 3B). At POD 1, mean CRP values (PFS group, 102.464 ± 17.027 mg/L; PFD group, 85.615 ± 12.604 mg/L) were approximately 15 times greater than at baseline (7.741 ± 2.57 mg/L) or in the PACU (5.778 ± 1.283 mg/L).

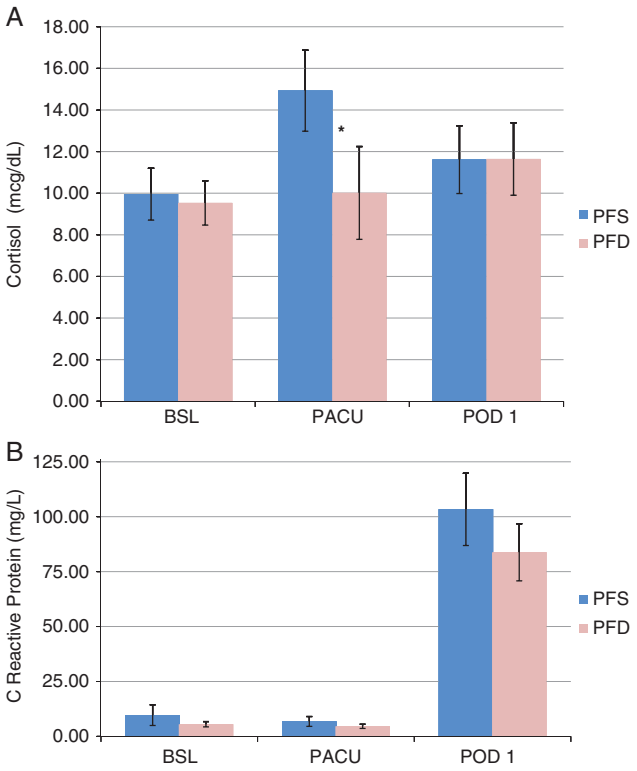

FIGURE 3. A, B. Plasma concentrations of cortisol and C-reactive proteins (CRP) preoperatively (BSL), immediately after surgery [postanesthesia care unit (PACU)], and on postoperative day (POD) 1. Cortisol levels were significantly higher in the PACU for the propofol/fentanyl/placebo-saline (PFS) group than in the propofol/fentanyl/dexmedetomidine (PFD) cohort ($P = 0.031$). At POD 1, mean CRP values were significantly greater than at baseline ($P = 0.026$) but without a significant difference between groups.

TABLE 2. Perioperative Cytokine Concentrations

Variables	Groups	Baseline (pg/mL), N	PACU (pg/mL), N	POD 1 (pg/mL), N
IL-1a	PFS	2.3 (1.4-4.2),16	2.5 (1.4-5.9),16	2.58 (1.4-2.6),17
	PFD	2.3 (1.4-3.2),15	2.4 (1.4-3.2),16	2.52 (1.4-3.6),15
IL-6	PFS	1.2 (1.2-1.2),6	3.7 (1.2-19.9),17	50.0 (11.2-82.1),27
	PFD	1.2 (1.2-3.9),8	9.4 (1.4-22.1),21	60.8(27.3-122.8),24
IL-8	PFS	4.1 (1.1-6.3),20	11.3 (2.1-23.1),23	16.4 (6.2-24.6),27
	PFD	6.9 (4.0-14.0),24	11.9 (7.6-23.8),23	20.9 (12.6-31.2),21
IL-10	PFS	1.11 (1.1-3.6),8	19.8 (5.6-55.5),23	9.3 (1.8-28.9),23
	PFD	1.11 (1.1-1.1),5	1.11 (1.1-9.0),12	13.3 (1.1-17.1),17
TNF-α	PFS	7.1 (1.3-10.2),21	7.4 (1.7-11.4),24	7.9 (2.1-11.4),22
	PFD	10.1 (6.9-12.6),24	10.2 (6.3-12.3),23	10.1 (3.8-12.7),21
IL-1b*	PFS	L (L-L),3	L (L-L),3	L (L-L),4
	PFD	L (L-L),0	L (L-L),0	L (L-L),0
IL-1ra	PFS	L (L-8.6),12	0.6 (L-10.31),14	L (L-24.5),12
	PFD	L (L-L),1	L (L-L),3	L (L-L),5
IL-12(p70)†	PFS	L (L-L),3	L (L-L),4	L (L-L),4
	PFD	L (L2.9),6	L (L-L),5	L (L-2.8),6
IL-2‡	PFS	L (L-L),1	L (LL),3	L (L-L),3
	PFD	L (L-L),1	L (L-L),2	L (L-L),2
		Median (25%-75%), N	Median (25%-75%), N	Median (25%-75%), N

*At 90th percentile, there is a distinction between PFD (all visits = "L") and PFS (visits = 3.034, 3.369, and 3.845, respectively).
†At 90th percentile, PFD values by visit, respectively, are 37.62, 50.18, and 53.74; and, PFS values are 10.75, 17.4, and 15.64.
‡At 90th percentile, PFD values by visit, respectively, are L, 0.33 and 0.72, and PFS values are L, 1.59 and 3.12.
"L" refers to concentration of the cytokine in a sample, which is below a limit of detection; "N" number of samples with the measurable level of cytokine.
IL indicates interleukin; PACU, postanesthesia care unit; PFD, propofol/fentanyl/dexmedetomidine; PFS, propofol/fentanyl/placebo-saline; POD, postoperative days; TNF, tumor necrosis factor.

Immune Response

Cytokine concentrations in many plasma samples were below the limit of detection (Table 2). IL-6 and IL-8 showed detectable response in about 80% of subjects in the PACU and in about 93% at POD 1. There was an increase by visit (surgical effect), with no impact of study drug. The median values for IL-6 and IL-8 were 1.21 and 5.01 pg/mL at BSL, 4.69 and 11.85 pg/mL in the PACU, and 55.75 and 18.35 pg/mL on POD 1, respectively.

IL-10 also increases after surgery in all patients. However, IL-10 values are significantly larger than PFD values at visit 2 (19.8 vs. 1.1 pg/mL, $P < 0.001$, rank analysis). By visit 3, IL-10 values in the PFS group had dropped below those of PFD but not significantly (9.27 vs. 13.30 pg/mL, $P = 0.427$). Thus, all 3 cytokine levels increased after surgery, but only IL-10 had a significant effect of drug with the peak PFS-IL-10 values in the PACU. There were no detectable time (surgery) or drug effects on other cytokines.

DISCUSSION

In this prospective, randomized trial we attempted to evaluate the association between the degree of intraoperative stress, the immune response, and the recovery characteristics after major spinal surgery. We demonstrated that DEX moderately enhanced early recovery of patients after surgery as measured by the QoR40 score and moderately reduced fatigue as measured by the FSS. Further, all quality of recovery domains were numerically consistent with the QoR40 total results, with the exception of DSF and DSB tests. However, a clinical significance of these effects is uncertain.

Plasma levels of cortisol immediately after surgery (in PACU) were lower in the PFD group but returned to baseline on POD 1. Concentrations of CRP were significantly higher after surgery in both groups on POD 1. There were postsurgical increases in IL-6, IL-8, and IL-10 levels in all patients. DEX did not differentially modulate levels of IL-6 or IL-8 but decreased the concentrations of IL-10 immediately after surgery. A reduced stress response as measured by cortisol concentration may have contributed to the enhanced recovery of patients treated with DEX. We could not detect differences in the inflammatory response between the 2 groups (other than IL-10) because of the variation of cytokine concentrations in our study. Moreover, cytokine levels were below levels of detectability in many samples.

A surgery-related increase in levels of stress hormones and inflammatory markers (eg, cytokines) has been well documented.[15] It has been suggested that the endocrine and inflammatory responses are responsible for a number of postoperative complications (eg, fatigue, delirium, and atrial fibrillation).[16–18] Modulation of the endocrine, metabolic, and/or inflammatory responses may reduce postsurgical fatigue and shorten the postoperative convalescence period.[19] Although our hypothesis is consistent with this research, a notion of negative role of stress response on perioperative outcome (at least in some settings) is argued by some investigators. For example, Zlotnik at el[20] recently demonstrated that suppression of a stress response is associated with worsening neurological outcome in the rat head trauma model.

Numerous methods have been evaluated to reduce surgery-associated increase in plasma level of stress hormones and/or to modulate immune reaction perioperatively.[21] However, most of these investigations have not attempted to establish an association between these responses and measurable clinical outcomes. Glucocorticoids are the only class of drugs that were systematically studied in that manner.[22] The advantages of perioperative treatment using steroids have been demonstrated in cardiac and abdominal surgery. The presented pilot clinical trial is the first investigation that evaluated a drug other than a steroid and attempted to correlate the levels of neuroendocrine and inflammatory biomarkers with measurable clinical outcomes.

DEX attenuated a significant elevation of cortisol immediately after surgery. The kinetics of cortisol change (peak at the immediate postoperative period with a return toward baseline on POD 1) in our study is consistent with findings of other investigators.[23] High levels of cortisol are observed in various chronic conditions, such as depression, anxiety, type 2 diabetes, hypertension, and chronic fatigue syndrome.[24] Moreover, there is an undisputed connection between high levels of cortisol and postoperative (or intensive care unit) delirium.[18] However, it is unclear whether the enhanced recovery in patients treated using DEX in our study is a result of changes in plasma cortisol concentration, because the largest difference in QoR40, MMSE, and FSS scores was observed on POD 3, whereas DEX suppressed cortisol production in the PACU only. Cortisol is a biomarker of the stress response. Although this teleologically developed response is a necessary component of the body's defense mechanisms, it is associated with the impairment of various mechanisms responsible for postoperative recovery. The utility of stress response in an elective surgical situation has been questioned by many.[25,26] It is possible that DEX reduces some aspects of the intraoperative stress response (as measured by cortisol levels), which, in turn, leads to enhanced recovery. However, this suggestion is highly speculative, as CRP, which is implicated in the production of sickness behavior, was elevated on POD 1 in all patients.

We could not establish a correlation between concentrations of cytokines and quality of recovery. We did find a significant rise in the plasma level of proinflammatory cytokines IL-6 and IL-8. Numerous investigators have observed similar changes postoperatively.[27,28] There were no intergroup differences. These results were somewhat unexpected, as DEX infusion significantly decreased levels of IL-6, IL-1, and TNF-α compared with propofol in mechanically ventilated patients 24 hours after ileus surgery.[6] Moreover, our results contradict the findings of Kim and Hahn[29] in 20 patients who reported that preoperative treatment using Clonidine 0.15 mg, an orally administered α-2 agonist, significantly reduced plasma levels of IL-6 3 hours after the start of surgery in patients undergoing total abdominal hysterectomy. This inconsistency may be explained by the more diverse population in our study (men and women vs. women only), less uniform surgery (multilevel spinal fusion vs. abdominal hysterectomy), or simply by the different effects of clonidine compared with DEX on the immune system. In addition, the quartile ranges of Kim and Hahn were significantly lower than ours. Both IL-6 and IL-8 have been implicated in the development of sickness behavior.[30] DEX decreased plasma concentration of IL-10, an anti-inflammatory cytokine, immediately after surgery. A role of IL-10 in inducing (or alleviating) sickness behavior has not been established and it is unclear whether this effect contributed to the enhanced recovery of patients in the PFD group. IL-1β and TNF-α are the main proinflammatory cytokines involved with sickness behavior.[31] Unfortunately, the results of plasma TNF-α were too scattered to make any meaningful conclusion, which is consistent with some reports.[32] Wu et al[33] reported no change in TNF-α after colorectal surgery in all patients irrespective of treatment (epidural clonidine vs. placebo). In contrast, Nader et al[34] found an increase in TNF-α concentration after surgery in their sample of 7 patients undergoing peripheral vascularization. It is most likely that the observed variability is again related to diverse patient populations and the extent of surgical trauma. Plasma concentrations of IL-1β, IL-1ra, IL-2, and IL-12 were lower than the detection limit of our methods in the majority of samples. These results are consistent with several clinical studies when investigators attempted to measure concentrations of these proteins using commercially available kits.[35]

There are 2 major limitations to this study: first, unexpectedly, we had a significantly different number of male and female patients in our sample. A number of studies have suggested different immune responses to surgery in men and women.[36,37] Although we assessed the effect of sex by resampling from our actual groups to generate groups with balanced sex populations (the bootstrapping technique), the issue of the unmatched samples cannot be ignored. The sex imbalance could explain the difference in baseline concentration of some cytokines. Second, the logistics of the trial (mostly financial constraints) precluded us from drawing blood samples on POD 2, 3, or 30. Thus, our conclusion regarding the effect of stress on the quality of recovery cannot be directly correlated with the level of biomarkers of neuroendocrine or immune response. Moreover, it was impractical to standardize postoperative pain management, because several surgical teams were responsible for the patients' care. Although all patients reported minimal pain before their neurobehavioral assessments, the effect of opioids on behavioral outcome cannot be ignored.

It is difficult to examine causality with a limited population and only 3 to 5 time points. However, we can make several conclusions on the basis of the results reported above. First, the behavioral responses are affected by the surgery at the earliest time measured (POD 1) and are all impaired. The differential responses due to drug group are generally significant on POD 3, although numerically the PFD scores show less impairment than do PFS at most postsurgical times before POD 30 (when scores have returned to baseline). Cytokines IL-6, IL-8,

and IL-10 all show elevation by the PACU measurement, as does cortisol. CRP has a large response by POD 1. The drug effect appears for both cortisol and IL-10 by the PACU measurement, which is earlier than our earliest time point for the behavioral studies. Our study did reveal an association between changes in concentrations of inflammatory markers and clinical outcomes. The drug effect on postoperative fatigue and quality of recovery is delayed, generally not reaching full significance until POD 3. Therefore, if the differential responses to drugs seen early on with the biomarkers contribute to the differential behavioral responses seen on POD 3, there must be a slow intervening process, which is differentially activated at the onset and continues through to POD 3, conveying the differential impact of the drugs.

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APPENDIX 1. MODIFIED FATIGUE SEVERITY SCALE (STATEMENTS IN THE ORIGINAL VERSION OF THE TEST ARE SHOWN IN *ITALICS*)

1. My motivation is lower when I am fatigued.
2. Getting out of bed brings on my fatigue *(Exercise brings on my fatigue)*.
3. I am easily fatigued (more than in my daily life outside the hospital) *(I am easily fatigued)*.
4. Fatigue interferes with my physical functioning.
5. Fatigue causes frequent problems for me.
6. My fatigue prevents sustained physical functioning required for rehabilitation *(My fatigue prevents sustained physical functioning)*.
7. Fatigue interferes with my ability to read and watch television *(Fatigue interferes with carrying out certain duties and responsibilities)*.
8. Fatigue is among my 3 most disabling symptoms.
9. Fatigue interferes with my interaction with friends and family (*Fatigue interferes with my work, family, or social life*).

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