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

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Abstract

Background—Surgery induces a variety of metabolic, endocrine and immune changes collectively known as the “stress response”, which often may lead to prolonged post-operative 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 with either propofol/fentanyl/dexmedetomidine (PFD) or propofol/fentanyl/placebo-saline (PFS). The quality of recovery (a primary end point) was assessed using a 40-item quality of recovery questionnaire (QoR40) and a 9 questions fatigue scale (FFS). The tests were administered preoperatively, on postoperative days (POD) 1, 2, 3 and 30. Blood samples were collected at baseline, in the post-anesthesia care unit (PACU) and POD 1 and were analyzed for levels of cortisol, C-reactive proteins (CRP) as well as the cytokines IL-1 α , IL-1 β , IL-1 α , IL-2, IL-6, IL-8, IL-10, and TNF α . Data were analyzed with SPSS software (version 18) using multivariate and mixed model approach to test for the effect of surgery and drug group. Pairwise comparisons were assessed with t-test or rank tests after correcting for multiple comparisons.

Results—The global QoR40 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 falling to lower values on POD 1 (163.63 ± 2.47) and POD 2 (170.94 ± 2.38) than on baseline (180.56 ± 1.588 , mean $\pm$ 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 FSS was detected on POD3 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 PACU while CRP levels were elevated on POD 1. DEX significantly reduced levels of cortisol but not CRP. Levels of cytokines IL-6, IL-8, and IL-10 levels 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.

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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 to control group. Our sample size was not sufficient to detect differences in either the incidence of complications or of clinically relevant outcomes.

Introduction

The association between the surgery induced neuroendocrine and inflammatory response, anesthetic management and both short- and long-term outcomes is increasingly recognized by the anesthesia community. Surgical injury to tissue causes a variety of profound physiologic reactions which are essential to the restoration of an organisms' homeostasis. The response involves a surge of stress hormones (i.e. C-Reactive Protein (CPR), cortisol, catecholamines), activation of the complement system, migration of leukocytes to the site of injury, the release of cytokines (e.g. interleukins, tumor necrosis factor) as well as other cellular products (i.e. superoxide radicals, proteases, growth factors) ¹⁻². An appropriate inflammatory cascade is essential for tissue reconstitution and infection control. Because of the 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 in the elderly, neonates, and patients with significant co-morbidity ³⁻⁵. Additionally, mediators of inflammation may induce fatigue and prolong convalescence in otherwise healthy patients. Thus, modulation of the immune response may reduce the incidence of post-operative 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 anesthetic technique may affect clinical outcomes by perturbing the balance between pro- and anti-inflammatory responses. It is well documented that dexmedetomidine (DEX) inhibits the neuroendocrine and inflammatory response in various experimental as well as clinical settings. Recent evidence suggests that DEX decreases 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 of plasma cytokine levels after endotoxin injection and drastically reduces the mortality rate of infected animals ⁷. These results suggest a role for DEX in preventing untoward stress responses, mitigating post-surgical convalescence and possibly of reducing the rate of complications during the convalescence period. However, thus far, there are 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 correlates with meaningful clinical outcomes. We measured circulating levels of cortisol, C-reactive proteins and cytokines (IL-1 α , IL-1 β , IL1ra, IL-2, IL-6, IL-8, IL-10, IL-12, and 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 scale (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/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 NYU School of Medicine and written informed consent, we enrolled 66 adult patients scheduled for elective multilevel lumbar fusion surgery. Exclusion criteria included cognitive impairment, chronic use of antipsychotic medications, treatment with alpha-2 agonists or antagonists within 2 weeks of study entry, chronic use of anti-inflammatory drugs (i.e. 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 group (double-blind design). The investigator who was unaware of the treatment group and was not involved in patients intraoperative care, performed postoperative evaluations.

Surgery and Anesthesia

General anesthesia was induced with propofol (1.5–2 mg/kg) and fentanyl (2–5 mcg/kg). Rocuronium (0.6 mg/kg) was used to facilitate endotracheal intubation. Patients were ventilated with an oxygen – air mixture ($FiO_2=0.4$) with PetCO₂ stabilized at 30–35 mm Hg. The study drug infusion began after placement of the IV line, was maintained throughout the case and stopped approximately 20 min before the end of surgery. The infusion rate was fixed at 0.5 mcg/kg/hr 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 BIS level of 45–50. Every patient had an arterial line. Phenylephrine and ephedrine (rather than the titration of the anesthetics) were used as needed to maintain mean arterial pressure between 70–90 mm Hg. All patients received ondansetron 4 mg prior to the end of surgery. Patients were awakened and extubated in the OR and transferred to the PACU upon following simple commands. In the PACU, all subjects who received rescue opioids as indicated by a Numeric Pain Rating Scale score > 2 or upon the subjects' request.

Data collection & blood sampling

Blood samples for the analysis of cortisol, CRP, and cytokines were collected prior to the induction of general anesthesia 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 –70C until analysis. Analyses for serum levels of CRP and cortisol were performed on the VITROS 5600 analyzer (Johnson and Johnson, Rochester, NY, USA) at the NYU 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 concentrations 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 anti-cortisol 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. Multi-analyte profiling was performed on the Luminex-200 system and the XMap Platform (Luminex Corporation). Calibration microspheres for classification, reporter readings as well as sheath fluid were purchased from the Luminex Corporation. Acquired fluorescence data were analyzed by 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 based upon software extrapolation of diluted standards.

Neurobehavioral assessments

A forty item previously validated questionnaire (QoR-40) was used to quantify quality of recovery⁸⁻⁹. 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 nine item FSS scale which is one of the most commonly used means of measuring fatigue¹⁰⁻¹¹. Five of those FSS items were modified to reflect the perioperative environment (see Appendix 1). A low FSS value (e.g. 1) indicates strong disagreement with the statement, whereas a high value (e.g. 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 their reported a level of pain less than 2.

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

Statistical analysis

The QoR-40 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 varied from 15 on day 1 to 20 on day 90 in spinal surgery patients. Myles et al recently demonstrated that patients with severe nausea and vomiting postoperatively had a 12 unit lower score than those without nausea and vomiting – a clinically meaningful outcome¹³. A SD of 17 and a sample size of 27 subjects per group would allow for detecting a 13 unit difference in QoR-40 scores assuming a two sided test with $\alpha=0.05$ and a power of 80%.

Continuous data were tested for normality using the Shapiro-Wilk tests for equality of distribution functions and reported as mean $\pm$ standard deviation (SD). Two-tailed t tests were used to compare equality of baseline characteristics and clinical data. Categorical parameters were compared using Chi-square tests or Fisher exact tests as appropriate. Because only few patients required vasoactive drugs intraoperatively and because doses of those drugs varied, the data is presented as numbers and proportions but not analyzed.

Mixed model and multivariate analysis was 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 ANOVA due to the inability to satisfy sphericity assumptions. The analysis looked at two issues: 1] whether there was a response to surgery ("visit"), and 2] whether there was a differential response to study drug ("randomization"). The co-factor 'gender' was not significant in the model and was dropped. In addition, we performed contrast analysis of pairwise comparisons of baseline values versus post surgical time frames of interest (Sidak multiple comparison correction by SPSS). In order to be responsive to potential deviations from normality, significant comparisons were confirmed with 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 with bootstrap techniques (re-sampling), since 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 “robust estimation”, we calculated the mean differences and 95% confidence intervals (percentile method) of 1000 re-sampled groups (n=28 subjects per group). In addition, we tested for the effect of gender by re-sampling from our actual groups to generate groups with balanced gender populations (n=14), which were then similarly analyzed.

Results

A total of 66 patients were recruited. However, twelve patients were excluded from the final analysis due to 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). One patient in the PFD group had a postoperative MI and was excluded from analysis (1). Thus, twenty eight patients in the PFS group and twenty six 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 reduced either fentanyl (524.1 ± 358.2 mcg vs 445.2 ± 230.7 mcg, $p=0.344$) or propofol (2153.7 ± 1258.6 mg vs 1545.6 ± 554.6 mg, $p=0.061$) requirements. Equal number of patients in each group required phenylephrine and/or ephedrine treatment (Table 1). The results could not be meaningfully analyzed due to the small number of entries. All 54 patients remained hemodynamically stable perioperatively and there were no reports of complications related to administration of anesthesia.

Quality of Recovery

Global QoR-40 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 BSL scores. Scores were significantly lower compared to baseline (BSL) on POD1 and POD 2 for both groups combined (-18.78 , $p < 0.001$; -9.61 , $p < 0.001$). QoR-40 values returned toward BSL on POD3 (-4.389 difference, $p=0.229$) continuing to show no difference for POD30 (3.056 difference, $p=0.171$). Although QoR40 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 POD3 (-13.74 , $p=0.005$).

Global QoR-40 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 one 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 which were still depressed compared to BSL at POD 2 (-2.63 , $p=0.038$; -3.074 , $p=0.015$; -2.796 , $p > 0.001$, respectively). The temporal profile of ‘comfort’, ‘emotion’ and ‘physical independence’ were all very similar to that of Global QoR40 – namely 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 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 ; $p=0.032$) 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 ($p=0.291$; Figure 2). Patients reported significantly higher levels of fatigue postoperatively (POD 1 through POD 3) compared to BSL (BSL-POD1= -20.94 ; BSL-POD2= -19.76 ; BSL-POD3= -18.17 ; $p<0.001$). By POD30, the difference was less (-11.46) and no longer significant ($p=0.058$). Patients in the PFD group had numerically lower scores at every post surgical evaluation and were significantly lower on POD3 by pairwise comparison PFD-PFS on POD2= -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 drug group.

Assessment of Cognitive Recovery

MMSE was measured only during hospitalization. It significantly dropped 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 units ($p=0.02$), so POD 1 was clearly different than 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 the PFS subjects. Thus DSF fell from 8.56 ± 0.40 to 7.67 ± 0.37 , and DSB fell from 5.26 ± 0.43 to 4.37 ± 0.37 for these patients ($p<0.05$).

Stress Response

Both, cortisol and CRP plasma concentrations increased after surgery. Cortisol levels (baseline 9.76 ± 0.825 mcg/dL, mean $\pm$ SE) were significantly higher in the PACU for the PFS group than in the PFD cohort (15.25 ± 1.99 mcg/dL 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 (Figure 3a). A rise in CRP levels was slowest and without statistically significant differences between groups (Figure 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 the baseline (7.741 ± 2.57 mg/L) or PACU (5.778 ± 1.283 mg/L).

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 POD1. 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 pg/ml and 5.01 pg/ml at the BSL, 4.69 pg/ml and 11.85 pg/ml in the PACU and 55.75 pg/ml and 18.35 pg/ml on POD1 respectively.

IL-10 also increases following 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 have fallen below those of PFD but not significantly (9.27 vs 13.30 pg/ml, $p = 0.427$). Thus, all three cytokines rise following

surgery, but only IL-10 has a significant effect of drug with the PFS IL-10 values peak in the PACU. There were no detectable time (surgery) or drug effects for 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. Furthermore, 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 POD1. Concentrations of CRP were significantly higher after surgery in both groups on POD1. There were post-surgical increases in IL-6, IL-8, and IL-10 levels in all subjects. DEX did not differentially modulate levels of IL-6 or IL-8, but decreased 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 two groups (other than IL-10) because of the variation of cytokine concentrations in our study. Moreover, cytokines levels were below levels of detectability in many samples.

A surgery related increase in levels of stress hormones and inflammatory markers (e.g. cytokines) is well documented¹⁵. It has been suggested that the endocrine and inflammatory response is responsible for a number of postoperative complications (e.g. fatigue, delirium, atrial fibrillation)^{16–18}. Modulation of the endocrine, metabolic and/or inflammatory responses may reduce postsurgical fatigue and shorten the postoperative convalescence period¹⁹. 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 et al recently demonstrated that suppression of a stress response is associated with worsening neurologic outcome in the rat head trauma model²⁰. Numerous methods have been evaluated to reduce surgery associated increase in plasma level of stress hormones and/or to modulate immune reaction perioperatively²¹. 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 fashion²². The advantages of perioperative treatment with 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 that attempted to correlate the level 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 towards baseline on POD1) in our study is consistent with findings of other investigators²³. High levels of cortisol are observed in various chronic conditions, such as depression, anxiety, type 2 diabetes, hypertension, and chronic fatigue syndrome²⁴. Moreover, there is an undisputed connection between high levels of cortisol and postoperative (or ICU) delirium¹⁸. However, it is unclear whether the enhanced recovery in patients treated with DEX in our study is a result of changes in plasma cortisol concentration, because the largest difference in QoR40, MSEE and FSS scores was observed on POD3, while 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 body defense mechanisms, it is associated with the impairment of various mechanisms responsible for postoperative recovery. The utility of the stress response in the 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, lead to enhanced recovery. However, this suggestion is highly speculative, as CRP, which is implicated in the production of sickness behavior, was elevated on POD1 in all patients.

We could not establish a correlation between concentrations of cytokines and a quality of recovery. We did find a significant rise in 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 level of IL-6, IL-1 and TNF α compared to propofol in mechanically ventilated patients at 24 hours after ileus surgery ⁶. Moreover, our results contradict findings of Kim et al in 20 patients who reported that preoperative treatment with Clonidine 0.15 mg, orally administered α -2 agonist, significantly reduced plasma levels of IL-6 at three hours after the start of surgery in patients undergoing total abdominal hysterectomy ²⁹. This inconsistency maybe explained by the more diverse population in our study (men and women versus women only), less uniform surgery (multilevel spinal fusion versus abdominal hysterectomy) or simply by the different effect of clonidine compared to DEX on the immune system. In addition, the quartiles ranges of Kim et al. 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 is not established and it is unclear whether this effect contributed to enhanced recovery of patients in the PFD group. IL-1 β and TNF α are the main pro-inflammatory 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 reported no change in TNF α following colorectal surgery in all patients irrespective of treatment (epidural clonidine versus placebo) ³³. On the other hand, Nader et al found an increase in TNF α concentration after surgery in their sample of 7 patients undergoing peripheral vascularization ³⁴. 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-1 β , IL-1 α , 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 two major limitations to this study: First, unexpectedly, we had a significantly different number of males and females 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 gender by re-sampling from our actual groups to generate groups with balanced gender populations (the bootstrapping technique), the issue of the unmatched samples cannot be ignored. The gender 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 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 patients' care. Although all patients reported minimal pain prior to 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 3–5 time points. However, we can make several conclusions based on 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 PFS at most post postsurgical times prior to 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 the postoperative fatigue and quality of recovery is delayed, generally not reaching full significance until POD 3. Therefore, if the differential response to drugs seen early on with the biomarkers contributes to the differential behavioral response 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 three most disabling symptoms.
9. Fatigue interferes with my interaction with friend and family (*Fatigues interferes with my work, family, or social life*)

Figure 1.

Changes in global 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 PFS group than in PFD group on POD 3 ($p=0.005$).

Figure 2.

Changes in Fatigue Severity Scores over time. Score showed a significant effect of time (surgery) ($p < 0.001$). Patients in the PFD group had numerically lower scores at every post surgical evaluation and were significantly lower on POD 3 by pairwise comparison PFD-PFS on POD2= -13.7 , $p = 0.035$).

Figure 3.

Figures 3a and 3b. Plasma concentrations of cortisol and CRP preoperatively (BSL), immediately after surgery (PACU) and on postoperative day 1 (POD1). Cortisol levels were significantly higher in the PACU for the PFS group than in the PFD cohort ($p=0.031$). At POD1 mean CRP values were significantly greater than at the baseline ($p=0.026$), but without a significant difference between groups.

Table 1

Baseline Characteristics and Perioperative Parameters

	PFS	PFD	P-Value(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/Astma	6	1	0.055
Thyroid disease	5	1	0.102
Medications			
Beta-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
<u>Vasoactive drugs</u>	<u>n(%), [mean admin dose] *</u>	<u>N(%), [mean admin dose]</u>	
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, minutes	246.2 (150.2)	203.3 (120.8)	0.255
Postoperative Nausea	7.1%	11.5%	0.218

	PFS	PFD	P-Value(2 tailed)
Hospital Stay, hours	133.5 (104.0)	103.9 (42.1)	0.182

Values are mean + SD. BMI=body mass index. ACEI/ARB = angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

* For the vasoactive drugs, where not all of subjects were dosed, the table gives an n [the number of patients receiving a dose], a % [the percent of the patients that received a dose], and a mean administered dose [the mean value of the administered doses]; patients who did not received a drug were not included in the calculation of the mean}.

Table 2

Perioperative Cytokine Concentrations

Variable	Group	Baseline(pg/ml)	PACU(pg/ml)	POD1(pg/ml)
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
TNFa	PFS	7.1 (1.3–10.2)	7.4 (1.7–11.4)	7.9 (2.1–11.4)
	PFD	10.1 (6.9–12.6)	10.2 (6.3–12.3)	10.1 (3.8–12.7)
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(L – 2.9),6	L(L – L),5	L(L – 2.8),6
IL-2 ***	PFS	L(L – L),1	L(L – L),3	L(L – L),3
	PFD	L(L – L),1	L(L – L),2	L(L – L),2
		Median (25–75%)	Median (25–75%)	Median (25–75%)

'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

* At 90th percentile, there is a distinction between PFD (all visits = 'L') and PFS (visits = 3.034, 3.369, 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.