Effect of nociception level-directed analgesic management on opioid usage in robot-assisted laparoscopic radical prostatectomy: a single-center single-blinded randomized controlled trial (NOLDOR study)

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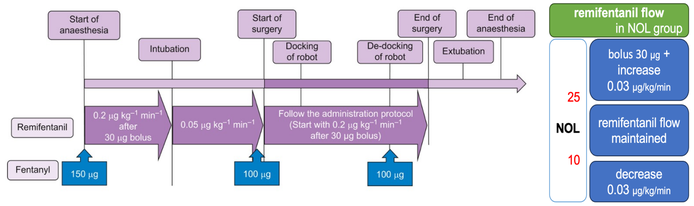
INTRODUCTION

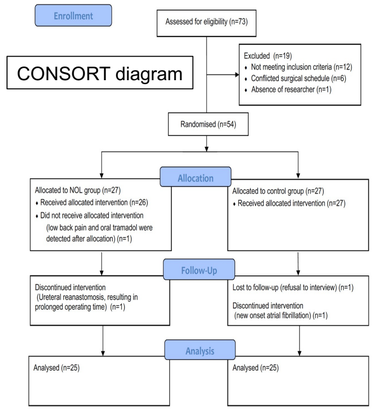
- Anesthetic management using Nociception Level (NOL) index provided by PMD-200 (Medasense Biometrics Ltd., Israel) reduced intraoperative opioid consumption and postoperative pain scores.[1,2]
- Funcke et al. reported an unintended increase in cortisol in the anesthesia management using NOL index or pupillometry at the compensation of remifentanil sparing.[1]
- Previous studies using NOL have assessed invasive stress with cortisol, but it has been suggested that interleukin-6 (**IL-6)** and C-reactive protein (**CRP)** may be more accurate than cortisol.[3]
- We hypothesized that the NOL-directed opioid protocol, guaranteeing the lowest infusion rate of remifentanil would provide for both opioid titration and prevention of increased invasive stress for patients.[4]

METHODS



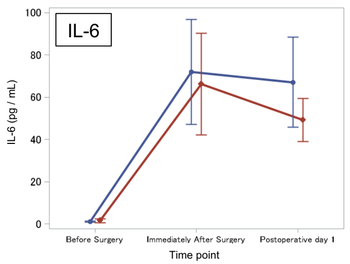
- Male patients scheduled for robot-assisted laparoscopic radical prostatectomy (RARP) with ASA-PS 1–3, aged 20–85 yr.
- Main exclusion criteria: preoperative chronic pain; regular medications of beta-blocker, oral steroids or opioids; arrhythmia / pacemaker; etc.
- Randomly assigned 1:1 to the NOL group (Figure) or the control group.
- The primary outcome was the mean intraoperative remifentanil infusion flow rate. (intraoperative remifentanil (μg) * ideal body weight(kg^{-1}) * operation time (min^{-1}))
- Secondary outcomes were
  - i. The plasma concentrations of IL-6, CRP, and cortisol
  - ii. Postoperative pain scores (NRS) 2 h postoperatively and on postoperative days 1, 2, 3, and 7.

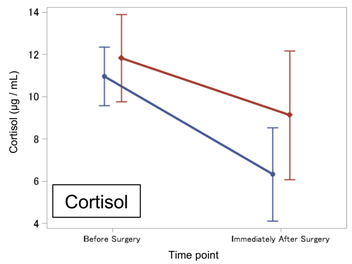
RESULTS

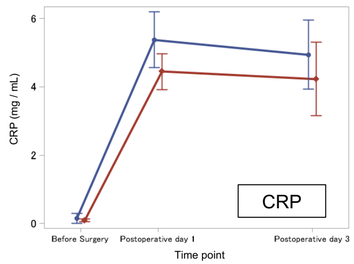


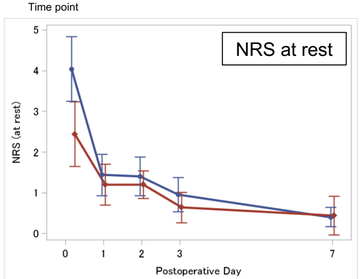
Patient characteristics	NOL group(n = 25)	Control group(n = 25)
Age (yr)	68 (6.6)	68 (5.8)
Weight (kg)	69.9 (9.7)	64.7 (8.6)
Height (cm)	169.8 (7.4)	166.5 (4.6)
BMI (kg m^{-2})	24.2 (3.2)	23.3 (2.8)
ASA-PS, n (%)		
I	3 (12.0)	3 (12.0)
II	21 (84.0)	22 (88.0)
III	1 (4.0)	0 (0.0)
Comorbidity, n (%)		
Hypertension	15 (60.0)	12 (48.0)
Diabetes	4 (16.0)	4 (16.0)
Chronic kidney disease	2 (8.0)	3 (12.0)
Duration of surgery (min)	261 (78)	259 (63)
Duration of anesthesia (min)	317 (79)	315 (64)

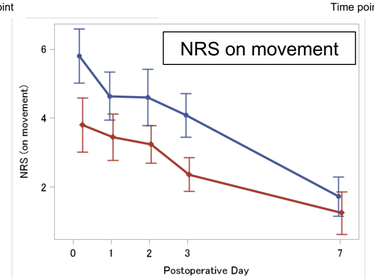
The primary and secondary outcome	NOL group (n = 25)	Control group (n = 25)	Mean difference (95%CI)	p-value
Intraoperative opioid amount				
Remifentanil (μg kg^{-1} min^{-1})	0.125 (0.017)	0.162 (0.049)	-0.038 (-0.059 to -0.017)	0.001
Fentanyl (μg/kg)	5.548 (0.48)	5.768 (0.623)	-0.220 (-0.537 to 0.097)	0.17

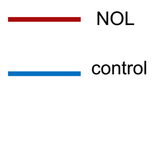












DISCUSSION

- Funcke et al. revealed unintended increase in cortisol at intraoperative remifentanil flow rates of less than 0.2 μg·kg^{-1}·min^{-1}, especially less than 0.1 μg·kg^{-1}·min^{-1}.[1] (Their protocol had allowed zero remifentanil.)
- Many studies using nociceptive monitor to control intraoperative remifentanil have been successful in reducing by 28–45%; however, no improvements in early post-operative NRS has been reported.[1,5,6]
- We had to use fentanyl in combination because the patients must return to the ward immediately after extubation. (Many centers in our country, including ours, do not have PACU.)
- Improvement in the postoperative NRS of pain in our study may be due to a mixture of intraoperative fentanyl and remifentanil.
- Our NOL-directed strategy led to a 20% reduction in remifentanil use and still did not increase serum inflammatory biomarkers; however, the difference in dosage was only 0.038 μg kg^{-1} min^{-1}.
- The importance of moment-to-moment control of intraoperative nociception with opioid may improve outcomes.[7]
- There was no statistically significant difference in IL-6; however, the mean difference of approximately 25% reduction in IL-6 in the NOL group and its clinical importance may warrant further investigation.

CONCLUSION

Our study demonstrated that NOL-directed analgesic management reduced remifentanil consumption by 20%, NRS at rest two hours postoperatively and NRS on movement up to postoperative day 3 without increase of serum inflammatory markers.

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