Pilot Study of Immune Response and Iatrogenic Withdrawal Syndrome in Critically-Ill Children Receiving Fentanyl Infusion

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Background

- Up to 57% of opioid-treated critically ill children developed opioid-associated iatrogenic withdrawal syndrome (IWS).
- Anesthesia and surgery can damage blood-brain barrier, allowing the infiltration of immune cells (e.g., monocytes) and impairing postsurgical neurocognition.
- Opioids may cause neuroinflammation through the peripheral immune system, contributing further to opioid tolerance and IWS.
- We *hypothesize* that a stronger monocyte inflammatory response is associated with opioid-associated IWS in critically-ill children receiving fentanyl infusion.

Objectives

- Evaluate the relationship between fentanyl use and the monocyte inflammatory response after ex vivo lipopolysaccharide (LPS) stimulation.
- Evaluate the relationship between the monocyte inflammatory response and the development of opioid-associated IWS.

Methods

Subjects and sample collection:

1 

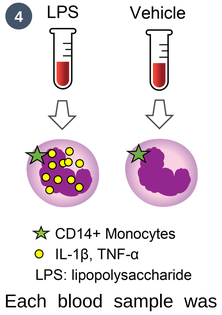
Postsurgical children <18 years requiring ventilator support and receiving fentanyl infusions.

2 

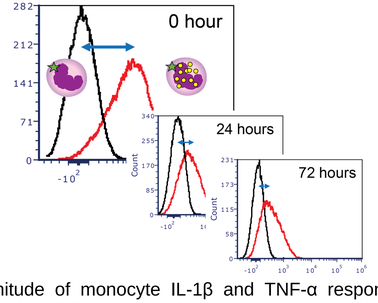
Blood sample collection

3 Demographics/clinical data, fentanyl and other sedative use, opioid-associated withdrawal syndrome were recorded.

Whole blood stimulation and flow cytometry:

4 

Each blood sample was divided: either treated with LPS or control.

5 

Magnitude of monocyte IL-1β and TNF-α response (red, with LPS stimulation) relative to control (black) was measured.

Relative changes of inflammatory response at 24 and 72 hrs:

6 $$\textbf{Fold change}^{*} = \frac{(\mathbf{Sig_{LPS} - Sig_{control}})_{\mathbf{24\ or\ 72\ hr}} - (\mathbf{Sig_{LPS} - Sig_{control}})_{\mathbf{baseline}}}{(\mathbf{Sig_{LPS} - Sig_{control}})_{\mathbf{baseline}}}$$

Fold change >1: stronger inflammatory response at 24 or 72 hr relative to baseline (0 hr)
Fold change <1: weaker inflammatory response at 24 or 72 hr relative to baseline

Results and Discussion

Patient Characteristics

Table: Patient characteristics and their association with IWS status

	No IWS (n=6)	IWS (n=7)		
	Median (Range) or Number (%)		OR (95% CI)[a]	P-value
Age (month)	4 (0-9)	0 (0-11)	0.864 (0.618-1.208)	0.39
PRISM 3	7 (2-16)	4 (0-12)	0.836 (0.628-1.113)	0.22
Fentanyl duration (hr)	25.1 (10.1-66.4)	93.5 (13.84-346)	1.032 (0.991-1.075)	0.13
Fentanyl 24-hour cumulative dose (µg/kg)	58.81 (25.68-128.64)	61.55 (54.74-183.43)	1.012 (0.985-1.038)	0.39
Fentanyl 72-hour cumulative dose (µg/kg)	278.68	302.85 (178.29-433.78)	1.001 (0.975-1.027)	0.96
Use of dexmedetomidine infusion	5 (83.3%)	1 (14.3%)	0.033 (0.002-0.68)	0.03
Use of midazolam repeated boluses	4 (66.47)	2 (28.57)	0.2 (0.019-2.118)	0.18
Monocyte IL-1β fold change from baseline				
24-hour	0.39 (0.12-0.67)	0.45 (0.28-1.05)	10.698 (0.059->999)	0.37
72-hour	0.1	0.4 (0.35-0.54)	>999 (<0.001->999)	0.80
Monocyte TNF-α fold change from baseline				
24-hour	0.13 (0.07-0.58)	0.29 (0.15-1.04)	21.286 (0.143->999)	0.23
72-hour	0.07	0.47 (0.34-0.58)	>999 (<0.001->999)	0.49

[a]Univariate logistic regression; OR: odds ratio; CI: confidence interval

Impact of Cumulative Fentanyl Dose on Inflammatory Response

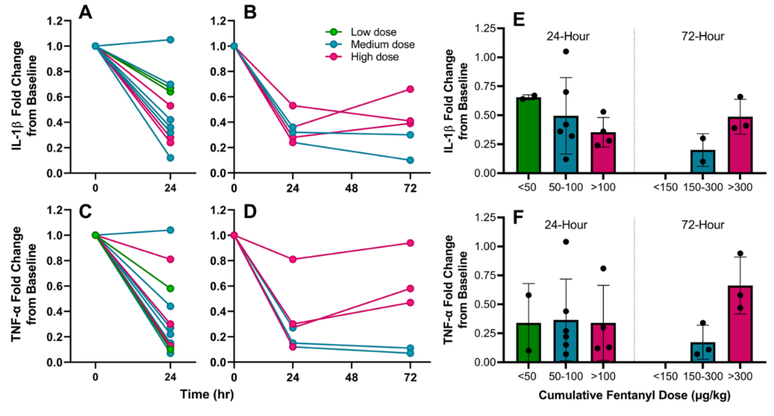


Figure 1: Individual patient's fold change of LPS-stimulated monocyte intracellular IL-1β (A and B) and TNF-α (C and D) response at 24 hours and 72 hours relative to baseline, based on cumulative fentanyl dose. Summary (mean and standard deviation) of monocyte intracellular IL-1β (E) and TNF-α (F) response. Low dose: 24-hour cumulative fentanyl dose <50 µg/kg or 72-hour dose <150 µg/kg; Medium dose: 24-hour 50-100 µg/kg or 72-hour dose 150-300 µg/kg; High dose: 24-hour >100 µg/kg or 72-hour >300 µg/kg.

▲ **Findings**:

- A trend for higher suppression of IL-1β response in monocytes at 24 hours in patients receiving higher fentanyl dose
- For those who received >72-hour of fentanyl infusion, both IL-1β and TNF-α were less suppressed at 72 hours among those who received a higher dose

◄ **Findings**:

- 6 of the 13 patients (46%) developed IWS.
- Among those who developed IWS, we observed a trend for younger age and longer fentanyl duration.
- Concomitant use of dexmedetomidine infusion was associated with lower odds of IWS.

Inflammatory Response and Opioid-Associated Iatrogenic Withdrawal Syndrome

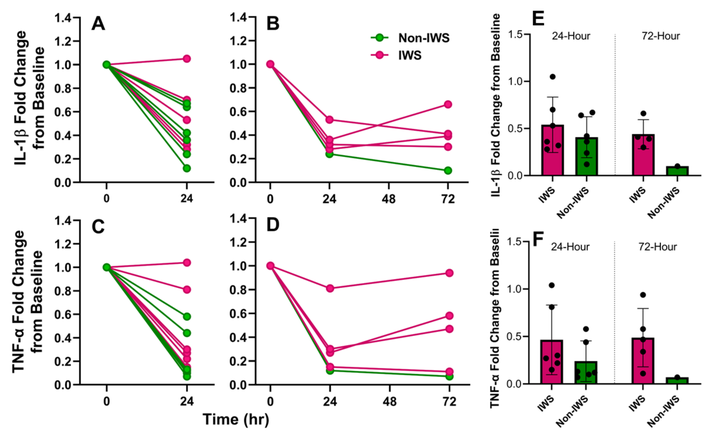


Figure 2: Individual patient's fold change of LPS-stimulated monocyte intracellular IL-1β and TNF-α response at 24 hours and 72 hours relative to baseline, based on the iatrogenic withdrawal syndrome (IWS) status. Summary (mean and standard deviation) of monocyte intracellular IL-1β (E) and TNF-α (F) response based on the IWS status and time points.

▲ **Findings**:

- A trend for a weaker immunosuppression at 24 and 72 hours observed among patients with IWS

Conclusions

- The suppression of the monocyte inflammatory response may depend on the fentanyl dose and duration, and a weaker suppression may be associated with the development of opioid-associated IWS.

Future Directions

- A larger sample size is needed to determine the relationship between inflammatory response and IWS.
- Due to the complex relationship among fentanyl exposure, dexmedetomidine use, and immune responses, there is a need to disentangle the impact of these factors on IWS and determining whether early inflammatory response can predict the development of IWS later or whether dexmedetomidine can prevent IWS.

References

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