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Research Article

Assessing Interleukin-6 as a Proxy of Perioperative Pain Intensity in Adolescents with Idiopathic Scoliosis Undergoing Spinal Fusion Surgery: An Exploratory Study

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Abstract

Introduction/Aim: The aim of this preliminary study was to assess the pro-inflammatory cytokine interleukin-6 (IL-6) as a physiological proxy of perioperative pain to allow for better targeting pharmacological intervention to adolescents with idiopathic scoliosis that do not respond well to the current standard of care.

Materials and Methods: Twenty-one patients scheduled for an elective spinal fusion surgery participated in the study. Patients reported their pain intensity and provided a blood sample before surgery, one day and two days after surgery (postoperative day 1 and 2 (POD1, POD2)), and 6 weeks after surgery. Concentrations of plasma IL-6 were quantified using a magnetic 30-plex assay (Life Technologies), in parallel to the C-Reactive Protein (CRP), a marker of inflammation. Repeated measure ANOVAs were used to identify changes in pain and IL-6 levels over time. Correlation analyses were performed to identify associations between the IL-6 concentration and the patient pain intensity at each timepoint. Mann Whitney test was used to see if patients reporting pain preoperatively had higher IL-6 levels than patients without pain.

Results: Forty-seven percent of patients reported having back pain before surgery. There was a significant effect of time on pain level and IL-6 levels, with an increase on POD1 and POD2 ($p<0.0008$) compared to baseline, and returned to baseline levels 6 weeks after surgery. An association was found between the pain intensity reported before surgery and the preoperative IL-6 levels ($r=0.614$, $p=0.003$), but not after the surgery ($p>0.05$). IL-6 concentration was significantly higher in patients reporting pain prior to surgery in comparison to patients reporting no pain (Mann-Whitney $U=12.50$, $p=0.0016$).

Discussion: These preliminary findings suggest that circulating IL-6 levels is not a quantifiable proxy for pain intensity after surgery but should be investigated furthermore as a proxy of pain in adolescents with idiopathic scoliosis.

Keywords: Adolescent idiopathic scoliosis; Cytokine; Inflammation; Interleukin-6; Perioperative pain

Introduction

Adolescent Idiopathic Scoliosis (AIS) is a three dimensional deformity of the spine affecting 1-3% of children between 10-16 years [1,2]. Patients with lateral curvature of a Cobb angle greater than 50° are recommended for spinal fusion surgery with instrumentation to correct the spinal deformity [3]. Spinal fusion surgeries are invasive orthopaedic procedures that cause a significant increase in acute postoperative pain intensity [4,5] that persists in 64% of patients 2 years after surgery along with 29.5% reporting continued analgesic use for back pain [6]. Furthermore, 35% of patients diagnosed with AIS experience significant pain prior to surgery [7]. The presence of preoperative pain has been observed to predict greater postoperative pain intensity in AIS patients [5], and greater preoperative pain intensity also predicted slower improvements in pain following spinal fusion surgery [8]. Previous studies have shown that inadequate postoperative pain relief can result in persistent post-surgical pain, significantly impairing quality of life [6,9].

Postoperative standard of care has now turned towards a multimodal approach to achieve proper analgesia through the synergistic properties of different analgesic classes [10]. It has been shown that the combination of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) in combination with opioid analgesics provided great efficacy in treating acute postoperative pain by targeting inflammatory processes [11]. This is due to the fact that pro-inflammatory cytokines are direct facilitators for the occurrence of surgical pain [12]. Following tissue injury, cytokines are released by immune cells in the local environment of afferent nerve fiber endings, thus sensitizing nociceptors and contributing to hyperalgesia [13]. Among the pro-inflammatory cytokines, Interleukin-6 (IL-6) has been shown to have an up-regulatory effect during acute inflammation and has been associated to surgical pain [14,15]. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are currently used to decrease pain, and their anti-inflammatory mechanism of action is mainly targeting the selective inhibition of the enzyme Cyclo-Oxygenase (COX) to reverse inflammation [16-18]. However, current postoperative pain management is still too often insufficient to alleviate the patient's pain, and it may result from the unspecificity of the treatment in targeting molecular mechanisms directly involved in the endogenous nociceptive processes.

The objective of this study was to assess IL-6 as a potential proxy of pain in adolescents undergoing spinal fusion surgery by analyzing its relationship with the self-reported perioperative pain intensity. We hypothesized that pain intensity and IL-6 levels would increase following a surgical insult and return to baseline levels 6 weeks after the surgery. We further hypothesized that high plasma levels of IL-6 would correlate with high self-reported pain intensity over the perioperative period. Such preliminary results were hypothesized to provide clinical significance to improve the perioperative pharmacological interventions proposed to our patients by investigating furthermore IL-6 specific targeting.

Materials and Methods

This study was conducted after obtaining ethics approval from the Research Ethics Board of McGill University (A05-M57-11B and A08-M71-14B). Patients were recruited from the outpatient clinic of the Shriners Hospitals for Children-Canada. Written informed consents were obtained prior to the beginning of the study.

Study participants

Patients aged between 12 and 18 years old, diagnosed with an Adolescent Idiopathic Scoliosis (AIS) and scheduled to undergo an elective spine surgery participated in the study. The exclusion criteria included adolescents who could not speak English or French, patients unable to complete the self-report measurement of pain intensity as a result of a diagnosed developmental delay (e.g. cognitive impairment), and patients with major chronic medical conditions (American Society of Anesthesiology status III or higher) [19].

Pain assessment and molecular analysis

Study variables were assessed at baseline (7-10 days prior to surgery), at postoperative day 1 (POD1, 24 hours after surgery) and postoperative day 2 (POD2, 48 hours after surgery), as well as at six weeks after surgery matching the standard of care follow-up visit with the treating surgeon. At each time point, patients were asked to report their pain intensity using a Numerical Rating Scale (NRS) from 0 (no pain) to 10 (worst pain imaginable) which has been validated for use in children [20]. Scores ranging from 1 to 3 indicate mild pain intensity, 4 to 6 indicate moderate pain intensity and 7 to 10 indicate severe pain intensity [21].

Subsequently, 10 ml of venous blood were collected in EDTA-coated tubes. The time of collection was recorded and blood samples were immediately centrifuged at 1200 g for 10 minutes at 4°C. Plasma was isolated and stored in microtubes at -80°C pending analysis. The IL-6 levels were assessed in triplicate and quantified using human cytokine magnetic 30-plex assay (cat. #LHC6003M, Life Technologies, Vienna, Austria), with a sensitivity of <0.5 pg/ml. The mean was calculated for each sample at each time point. To confirm the presence of inflammation, C-Reactive Protein (CRP) plasma concentrations were also quantified using commercially available enzyme-linked immunosorbent assay kit (cat. #10011236, Cayman Chemicals, Ann Arbor, United States) with a detection range of 46.9-3000 pg/ml. Both procedures were conducted following the manufacturer's instructions.

Anesthetics and analgesics in postoperative pain management

All patients undergoing spinal fusion surgery followed the institutional perioperative anesthesia, surgical, and spinal cord monitoring protocols. The anesthesia protocol was standardized to include total intravenous anesthesia with propofol and remifentanil or sufentanil, ketamine, and dexamethasone. After induction, all patients received a single injection of spinal morphine (0.005 mg/kg).

The postoperative pain management was standardized for the study purposes and included morphine and ketamine patient-controlled analgesia (PCA, bolus 1/1 mg) upon arrival to the post anesthesia care unit (PACU) with a starting bolus dose of 20 mg/kg, lockout 6 minutes and a 4 hours' maximum dose up to 0.4 mg/kg. The NSAID ketorolac was provided to the patients based on the individual decision of the treating anesthesiologist. Medication administration and time of administration were extracted from the patient medical charts.

Statistical Analysis

Normality of data was assessed using the Shapiro-Wilk test. Non-parametric repeated-measures ANOVA (Kruskal-Wallis test) followed by Dunn's multiple comparisons test to assess differences in time for pain intensity, IL-6 and CRP levels. Due to the non-parametric characteristics of IL-6 plasma levels, Spearman's Rho-rank statistics were used for correlative analyses between perioperative IL-6 concentrations and patient pain intensity. In order to control for the effect of NSAIDs on postoperative IL-6 levels and pain, partial correlations were used for correlative analyses between postoperative IL-6 levels and pain with NSAIDs dosage as a covariate in the analysis. IL-6 levels being a non-parametric variable, Mann-Whitney tests were used to analyze differences in IL-6 concentration between patients reporting pain and no pain preoperatively.

Power analysis was performed using G*Power 3.1 software. An estimated sample size of 19 patients revealed to provide 95% power and a two-sided alpha value of 0.05 for this preliminary study on AIS patients. Data analysis was performed using SPSS software package (IBM SPSS Statistics Version 24.0, Chicago, United States). A two-tailed p value of less than 0.05 was considered statistically significant.

Results

Patient Characteristics

Twenty-one participants were included in this exploratory study, with a majority of female patients. All patients completed the study measurements over the 4 timepoints and measures were collected, with the exception of 5 blood samples that could not be collected on POD1 due to coordination issues.

Almost half of the cohort reported experiencing back pain prior to their surgery. Patients reporting preoperative pain had an average pain score of 2.5±1.1 with a range between 1.0 and 4.0 on the NRS at baseline. Non-parametric Spearman correlations revealed no associations between baseline IL-6 levels and age ($p=0.2400$) or weight ($p=0.1831$). Mann-Whitney tests revealed no significant difference in baseline IL-6 levels between gender ($p>0.9999$), as well. All patients underwent a posterior spinal fusion with instrumentation either across the thoracic and/or the lumbar spine. Two patients received the Non-Steroidal Anti-Inflammatory Drug (NSAID) ketorolac on POD1 at least 6 hours before blood was collected. Six patients received ketorolac at least 6 hours before blood collection on the POD2 timepoint. None of the patients received ibuprofen prior to blood collection on either POD1 or POD2.

Pain intensity over the perioperative period

A mean score pain intensity of 1.2±1.5 on the 0-10 numerical rating scale was observed with all 21 patients at baseline. Patient's pain intensity increased significantly on POD1 (4.0±1.4) and POD2 (3.6±1.8) from baseline ($p=0.0002$ and $p=0.0008$ respectively, Figure 1A). Six weeks after surgery, patient's average pain intensity decreased and returned to baseline levels, with no significant variation in pain intensity between the two time points ($p>0.05$).

Perioperative molecular levels

Baseline plasma IL-6 concentration was 3.5±2.9 pg/ml. Plasma IL-6 increased significantly in all patients on POD1 (129.2±69.3 pg/ml) and POD2 (114.5±107.3 pg/ml) before returning to baseline levels 6 weeks after surgery ($p<0.0001$, Figure 1B). Baseline plasma CRP concentration was 1.3±2.9 µg/ml. Plasma CRP levels increased significantly on POD1 (144.8±200.5 µg/ml) and POD2 (313.2±614.5 µg/ml) before returning to baseline levels 6 weeks after surgery ($p<0.0001$, Figure 1C).

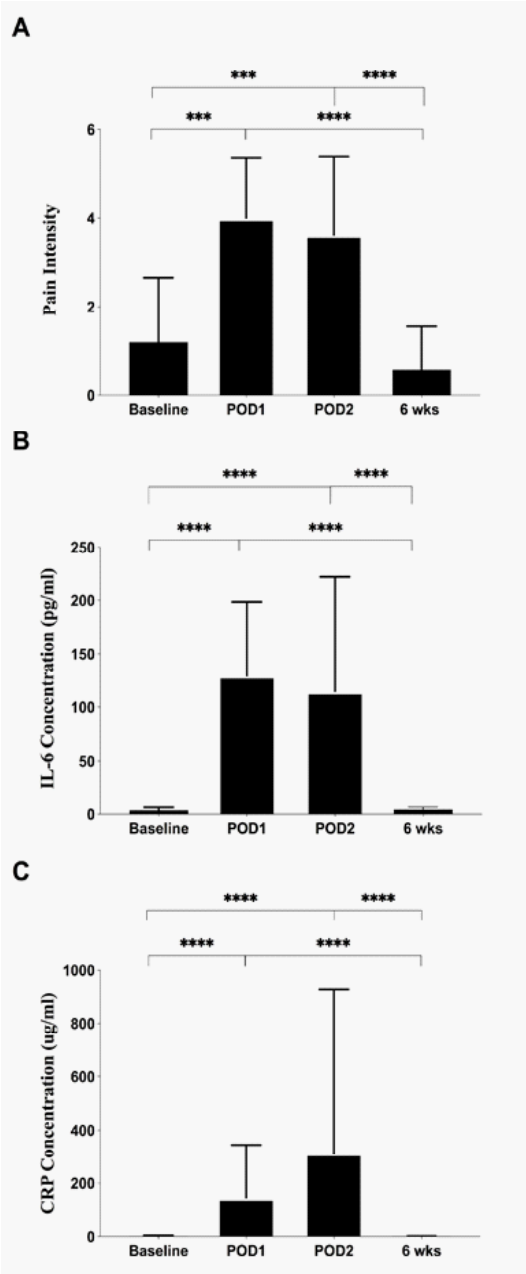

Figure 1: Average pain intensity, IL-6 and CRP levels measured throughout the perioperative period. A) A significant increase in average pain intensity is seen on POD1 (p=0.0002) and POD2 (p=0.0008) before decreasing to baseline levels 6 weeks after surgery (n=21). **B)** Plasma IL-6 levels were shown to increase significantly on POD1 (p<0.0001) and POD2 (p<0.0001) before returning to baseline levels 6 weeks after surgery (n=21). **C)** Plasma CRP levels were shown to increase significantly on POD1 (p<0.0001) and POD2 (p<0.0001) before returning to baseline levels 6 weeks after surgery (n=21). (Data expressed as Mean ± SD. ***= p<0.001, ****= p<0.0001). POD1: Postoperative Day 1; POD2: Postoperative Day 2; 6 wks = 6 weeks after surgery.

Association between perioperative plasma IL-6 levels and pain intensity

A moderate positive association was found between baseline plasma IL-6 levels and baseline pain intensity ((r=0.614, p=0.003, Figure 2). However, no other associations were observed at any of the postoperative time points, either at 24 hours (r=-0.3820, p=0.1444), 48 hours (r=-0.0747, p=0.7476) or 6 weeks (r=0.2558, p=0.2631) after surgery. Partial correlations, while controlling for ketorolac intake, also showed no association between IL-6 concentrations and pain intensity 24 hours (r=-0.3510, p=0.1990) or 48 hours (r=-0.1010, p=0.6710) after surgery. Mann-Whitney tests revealed a significant difference between patients with and without preoperative pain (Mann-Whitney U=12.50, p=0.0016). Patients with preoperative pain (score greater than 0) had higher levels of plasma IL-6 (5.4±2.9 pg/ml) in comparison to patients without preoperative pain (1.8±1.6 pg/ml) (Figure 3).

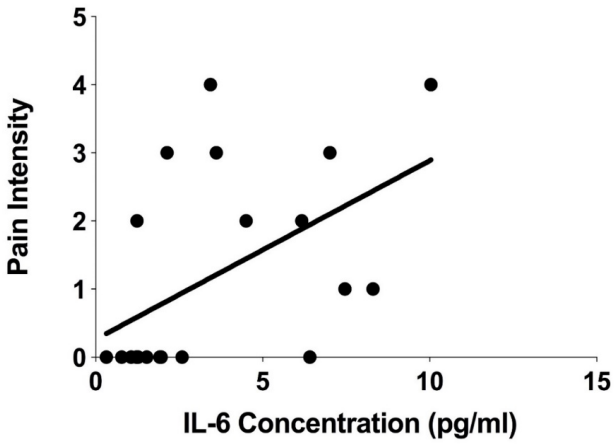

Figure 2: Association between baseline plasma IL-6 levels and pain intensity. A moderate, positive correlation (r=0.614, p=0.003) is observed between baseline plasma IL-6 levels and baseline average pain intensity (n=21).

Figure 3: Baseline plasma IL-6 levels of patients with and without preoperative pain intensity. Patients with preoperative pain had higher levels of plasma IL-6 (5.4±2.9 pg/ml) in comparison to patients without preoperative pain (1.8±1.6 pg/ml, p=0.0016) (n=21). (Data expressed as mean ± SD. **= p<0.01).

Discussion

Adolescent patients who underwent spinal fusion surgery reported experiencing an increase in pain intensity 24 hours and 48 hours after surgery, which returned to baseline levels 6 weeks after surgery. The results confirmed the hypothesis that plasma IL-6 levels would rise following a surgical insult in the acute postoperative period (POD1 and POD2) before decreasing back to baseline levels six weeks after surgery. The inflammation process was also confirmed by a similar result for the CRP levels, suggesting that the invasive nature of the surgery causes an upregulation of pro-inflammatory processes involving IL-6.

We also hypothesized that high pain intensity would correlate with high levels of plasma IL-6. Baseline plasma IL-6 levels and preoperative pain intensity of the patients were associated, but no correlation was observed between IL-6 and pain intensity after surgery. This may have occurred due to the fact that two of the patients received ketorolac on POD1 and six on POD2 at least 4-6 hours before blood collection. Ketorolac has an elimination half-life of 4-6 hours, and in the postoperative period it has been shown to downregulate IL-6 production following surgical wounds from caesarean deliveries and oral surgeries involving the tooth removal [22-24]. This may have skewed results because six patients received ketorolac prior to blood collection on POD2 and only one of these patients reported severe pain, three reported moderate pain and two reported mild pain on POD2. Following orthopaedic surgery in paediatric patients, ketorolac has been shown to cause a greater decrease in pain scores postoperatively in comparison to morphine alone [25], and thus, it is possible these patients reporting mild to moderate pain after ketorolac administration in our cohort may have had higher pain scores without ketorolac administration. We attempt to control for the effect of ketorolac on POD1 and POD2 on IL-6 concentrations and pain intensity by adding the doses of ketorolac given to patients at least 6 hours prior to blood collection as a co-variate in our partial correlations. However, the effect of the duration of time, within the 6-hour cut-off, between ketorolac administration and blood collection could not be accounted for in this analysis. Furthermore, the effect of ketorolac on the actual change in a patient's pain experience prior to and after ketorolac administration cannot be accounted for in this analysis, as well.

Although a correlation between plasma IL-6 and pain after surgery was not observed, there was a moderate positive correlation between baseline IL-6 levels and pain before surgery. These results are in agreement with the findings observed in a recent publication where preoperative IL-6 levels correlated with preoperative pain in adult patients scheduled to undergo total knee arthroplasty [26]. In their study, the authors also hypothesized that high postoperative serum IL-6 levels would be associated with high pain scores, and concluded that no associations were found. Therefore, it was suggested that the elevated cytokine levels may have a role in contributing to the chronic preoperative pain rather than the acute postoperative pain. In our cohort of AIS patients, we observed that 10 of the 21 patients came to their baseline timepoint with preoperative pain, and these patients had significantly higher levels of IL-6 in comparison to the patients with no preoperative pain. In a previous publication from our team, it was noted that 47% of AIS patients scheduled for spinal fusion surgery had reported sporadic episodes of back pain preoperatively [5]. A previous study has also shown that back pain affects three-quarters of AIS patients prior to surgery, and AIS has also been observed to be a possible risk factor in the development of paediatric low back pain [6,27,28]. Back pain is a common cause of chronic Musculoskeletal (MSK) pain in youth [29], and therefore, the role of IL-6 in the pathophysiology of paediatric chronic MSK pain may need to be explored further. Analyzing IL-6 levels in pediatric chronic MSK pain patients in comparison to a healthy pediatric cohort could help further validate IL-6 as a possible proxy of chronic MSK pain to be pharmacologically targeted.

Lastly, this was an exploratory study and the sample size should be increased to draw any conclusion of the results. Another limitation of this preliminary study resides in the quantification of the circulating molecule, being affected by various covariates related to the surgical experience such as the anesthetics and analgesics intake, as well as the surgical stress induced. An alternative approach would be to test the same hypotheses but by assessing the mRNA levels of IL-6 in the peripheral blood mononuclear cells, along with the plasma IL-6 protein analysis. This may provide more accuracy in the results of the postoperative levels of these inflammatory mediators due to the fact that stable mRNAs usually have longer half-lives than the protein themselves

[30]. In this study there was large variation in the plasma IL-6 protein levels on POD1 and POD2, and adding the IL-6 mRNA analysis would indicate if this large variation is replicated in the transcription of IL-6 as well. Thus, this would further validate the results obtained in this study. This would better highlight whether IL-6 is involved in the pathophysiology of chronic MSK pain in the pediatric population or whether it is just a marker of inflammation that is upregulated in response to the inflammatory processes involved with the invasiveness of orthopedic surgeries.

Conclusion

In conclusion, this study revealed that circulating IL-6 is not a proxy of perioperative pain in patients scheduled to undergo spinal fusion surgery and may not be a viable pharmacological target for pain postoperatively. However, an association between IL-6 and pain intensity before surgery was observed, with higher IL-6 in patients reporting back pain. Thus, more work should be done to assess the validity of IL-6 as a possible proxy of pain in adolescents with MSK pain compared to healthy controls.

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Disclosures

The authors have no conflicts of interest to declare. The McGill Scoliosis & Spine Research Chair and the Shriners Hospitals financially supported this study.

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