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ARAŞTIRMA MAKALESİ

Temporal Dynamics of Serum Interleukin-1 Beta Following Experimental Traumatic Brain Injury in Rats Running title: Serum IL-1β in TBI

Deneysel Travmatik Beyin Hasarı Modelinde Serum İnterlökin-1 Beta'nın Zaman İçindeki Değişimi

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SUMMARY

Aim: Traumatic brain injury (TBI) triggers complex inflammatory cascades, with interleukin-1 beta (IL-1β) identified as a key mediator of secondary neuronal damage. Although the role of IL-1β in neuroinflammation is well recognized, its dynamic profile in the peripheral circulation remains insufficiently characterized. This study aimed to assess serum IL-1β levels at defined intervals following experimental TBI in rats to elucidate its biomarker potential and therapeutic relevance.

Material and Methods: A total of 40 adult male Sprague-Dawley rats were randomly allocated into five groups (n=8/group): one sham group and four trauma groups corresponding to 1, 6, 24, and 72 hours post-injury. Moderate TBI was induced using the Marmarou weight-drop model (a 450-g weight dropped from a height of 2 meters). Serum IL-1β concentrations were measured by ELISA, and statistical comparisons were made using one-way ANOVA with Tukey's post hoc test.

Results: In the sham group, serum IL-1β showed a biphasic trend: an initial decrease at 6 hours, followed by partial recovery by 72 hours. In contrast, the trauma group exhibited a dynamic pattern: IL-1β decreased at 6 hours (p=0.0356), peaked significantly at 24 hours (p=0.0004 vs. 6h), and declined again by 72 hours. Between-group comparisons revealed significantly elevated IL-1β levels in the trauma group at 24 hours (p=0.0157) compared to sham.

Conclusion: Our findings suggest that serum IL-1β exhibits a temporally regulated expression pattern after TBI, with a peak at 24 hours representing a potential window for therapeutic targeting. IL-1β may serve as a minimally invasive biomarker to monitor post-traumatic inflammation, although correlation with functional outcomes and central tissue levels warrants further investigation.

Keywords: Biomarker; IL-1β; Neuroinflammation; Serum cytokines; Traumatic brain injury

ÖZET

Amaç: Travmatik beyin hasarı (TBH), sekonder nöronal hasarın temel aracısı olarak tanımlanan interlökin-1 beta'nın (IL-1β) rol aldığı karmaşık inflamatuvar kaskadları tetikler. IL-1β'nin nöroenflamasyondaki rolü iyi bilinmesine rağmen, periferik dolaşımdaki dinamik profili yeterince karakterize edilmemiştir. Bu çalışmada, ratlarda deneysel TBI sonrası belirli zaman aralıklarında serum IL-1β düzeylerinin değerlendirilmesi ile bu biyobelirtecin potansiyelinin ve terapötik öneminin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Toplam 40 erişkin erkek Sprague-Dawley sıçan rastgele beş gruba (n=8/grup) ayrıldı: bir sham grubu ve travmadan sonra 1, 6, 24 ve 72. saatlere karşılık gelen dört travma grubu. Orta dereceli TBH, Marmarou ağırlık düşürme modeli kullanılarak oluşturuldu (2 metre yükseklikten bırakılan 450 gramlık bir ağırlık ile). Serum IL-1β konsantrasyonları ELISA yöntemi ile ölçüldü ve istatistiksel karşılaştırmalar tek yönlü ANOVA ve Tukey post-hoc testi ile yapıldı.

Bulgular: Sham grubunda serum IL-1β iki fazlı bir eğilim gösterdi: 6. saatte başlangıçta düşüş, 72. saatte ise kısmi toparlanma. Travma grubunda ise dinamik bir patern izlendi: IL-1β 6. saatte azaldı (p=0.0356), 24. saatte anlamlı düzeyde yükseliş gösterdi (p=0.0004, 6. saat ile karşılaştırıldığında) ve 72. saatte tekrar azaldı. Gruplar arası karşılaştırmalarda ise, travma grubunda 24. saatte IL-1β düzeylerinin sham grubuna göre anlamlı şekilde yüksek olduğu saptandı (p=0.0157).

Sonuç: Bulgularımız, TBH sonrası serum IL-1β'nın zamana bağlı düzenlenmiş bir ekspresyon paterni sergilediğini ve 24. saatteki yükselişin terapötik hedefleme için potansiyel bir pencere olabileceğini göstermektedir. IL-1β, post-travmatik inflamasyonun izlenmesinde minimal invaziv bir biyobelirteç olarak kullanılabilir, ancak fonksiyonel sonuçlar ve santral doku düzeyleri ile korelasyonunun da araştırılması gerekmektedir.

Anahtar Kelimeler: Biyobelirteç; IL-1β; Nöroenflamasyon; Serum sitokinleri; Travmatik beyin hasarı

INTRODUCTION

Traumatic brain injury (TBI) remains a major cause of morbidity and mortality worldwide, especially among individuals under the age of 45. It is characterized not only by an immediate mechanical insult but also by a cascade of secondary injury mechanisms, which significantly contribute to neurological dysfunction and poor long-term outcomes (1).

One of the most critical components of secondary injury is neuroinflammation, driven largely by the rapid activation of microglia and subsequent release of pro-inflammatory cytokines. Among these, interleukin-1 beta (IL-1β) plays a pivotal role. IL-1β is rapidly upregulated following TBI and contributes to blood–brain barrier disruption, leukocyte infiltration, astrocyte activation, and neuronal damage (2–4). The temporal pattern and magnitude of IL-1β release have been associated with both the severity of injury and subsequent cognitive deficits (5).

Experimental studies have shown that IL-1β is detectable in brain parenchyma and serum within hours following TBI. For instance, Fan et al. demonstrated IL-1β mRNA expression in injured cortical and hippocampal tissues as early as 1 hour post-injury, with peak levels observed within 6 to 24 hours (6). Similarly, Raghupathi et al. reported early gene expression of IL-1β and TNF-α in cortical regions within the first hour, highlighting the rapid transcriptional response to trauma (4).

IL-1β not only contributes to acute neuronal injury but also interferes with long-term potentiation, a fundamental mechanism of learning and memory. Decreased cognitive performance following TBI has been linked to elevated serum IL-1β levels, particularly in mild injuries where structural changes may be subtle or absent (5).

Recent advances have identified the NLRP3 inflammasome as a key upstream regulator of IL-1β maturation, and its activation is now considered a hallmark of TBI-induced sterile inflammation (7,8). Inhibiting the NLRP3/caspase-1 axis or targeting IL-1β directly has shown promise in reducing neuroinflammation and improving neurological outcomes in rodent models (9,10).

Despite substantial progress in understanding the mechanisms of IL-1β activation and its deleterious effects, the temporal profile of serum IL-1β following TBI—particularly in standardized experimental models—remains insufficiently characterized. Clarifying this time-dependent expression pattern is crucial for evaluating its diagnostic value, identifying therapeutic windows, and guiding the timing of anti-inflammatory interventions.

In this study, we aimed to investigate the temporal changes in serum IL-1β concentrations following experimental moderate TBI in rats, using the Marmarou weight-drop model. By profiling IL-1β at multiple post-injury time points, we sought to characterize its dynamic expression and assess its potential as a biomarker for early post-traumatic inflammation.

MATERIAL AND METHODS

Animals: A total of 40 adult male Sprague-Dawley rats (weight: 250–300 g) were used in this study. The animals were housed in standard laboratory conditions (12 h light/dark cycle, 22 ± 2°C, 50% humidity) with free access to food and water. All procedures were conducted in accordance with the European Union Directive 2010/63/EU for animal experiments and approved by the Animal Ethics Committee of the Yeditepe University Faculty of Medicine, Istanbul, Turkey.

Experimental Groups and Study Design: The animals were randomly divided into five groups, each comprising eight rats. The sham group received only anesthesia without induction of trauma. The remaining four groups were subjected to experimental traumatic brain injury and were sacrificed at 1, 6, 24, and 72 hours post-injury, respectively, to allow for temporal evaluation of serum IL-1β levels.

Traumatic Brain Injury Induction: TBI was induced using the Marmarou weight-drop (impact acceleration) model, as originally described by Marmarou et al. and subsequently adapted in experimental rat studies (11–13). This method allows the induction of graded severities of TBI by altering the drop height (1.0–2.1 m) and the weight of the impactor (13). All components of the chosen model, including the impact weight, fall height, and the thickness of the foam bed, were optimized to produce a moderate diffuse brain injury. Under intraperitoneal anesthesia with ketamine (75 mg/kg) and xylazine (10 mg/kg), a midline scalp incision was made, and a stainless steel disc (10 mm diameter, 3 mm thickness) was placed over the skull between the bregma and lambda. In brief, a 450 g brass weight was dropped from a height of 2 meters through a vertical Plexiglas tube onto the disc affixed to the skull, while the animal lay on a foam bed to prevent skull fracture and rebound injury (13,14). Sham animals underwent the same procedure without the weight drop.

Blood Collection and Serum Preparation: At the end of the experimental period, 40 surviving rats (distributed across all designated time points) were sacrificed under deep anesthesia. Blood samples were obtained via cardiac puncture, collected in serum separator tubes, and centrifuged at 3000 rpm for 10 minutes at 4°C. The resulting sera were stored at –80°C until further analysis.

Measurement of Serum IL-1β: Serum IL-1β levels were quantified using a commercially available enzyme-linked immunosorbent assay (ELISA) kit specific for rat IL-1β (Rat IL-1 beta ELISA Kit, Invitrogen, Cat. No. BMS630, Bioassay Technology Laboratory, Shanghai, China), following the manufacturer's instructions. All samples and standards were run in duplicate. Optical density was measured at 450 nm using a microplate reader, and cytokine concentrations were calculated using a standard curve generated by curve-fitting software.

Statistical Analysis: Data were analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as mean ±standard deviation (SD) or median

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and range for continuous variables. The normality of data distribution was assessed using the Shapiro–Wilk test, and homogeneity of variances was evaluated with Levene's test. One-way analysis of variance (ANOVA) followed by Tukey's post hoc test was used to compare serum IL-1β levels among groups. A p-value < 0.05 was considered statistically significant.

RESULTS

Serum IL-1β levels demonstrated distinct temporal patterns in both sham and trauma groups over the 72-hour observation period (*Table 1*). These findings are visualized in *Figure 1*, which illustrates the dynamic temporal expression of serum IL-1β across both experimental conditions.

In the sham group, IL-1β concentrations exhibited a biphasic trend. At 1 hour post-anesthesia, the mean serum IL-1β level was 64.43 ± 13.28 pg/mL, which significantly decreased to 44.87 ± 15.35 pg/mL at 6 hours (p = 0.0232). Levels remained relatively stable at 24 hours (46.26 ± 9.30 pg/mL) compared to 6 hours, with a significant difference between 1 hour and 24 hours (p = 0.0211). By 72 hours, IL-1β levels increased again to 56.60 ± 12.24 pg/mL; however, the rises from 6 to 72 hours and from 24 to 72 hours did not reach statistical significance (*p = 0.1795; p = 0.1636*, respectively). These variations, despite the absence of injury, may reflect physiological fluctuations associated with handling, anesthesia, or circadian cytokine regulation. In the trauma group, IL-1β levels showed a dynamic temporal profile. An initial decrease was observed from 49.03 ± 8.79 pg/mL at 1 hour to 38.75 ± 7.71 pg/mL at 6 hours (p = 0.0356), followed by a marked increase at 24 hours (65.45 ± 13.22 pg/mL), which was significantly higher than both the 1-hour (p = 0.0161) and 6-hour (p = 0.0004) levels. By 72 hours, IL-1β levels decreased again to 53.68 ± 7.40 pg/mL, significantly lower than the 24-hour peak (p = 0.0024), but comparable to 1-hour values (p = 0.3026). This pattern suggests a transient proinflammatory surge peaking at 24 hours post-injury.

Direct comparisons between the sham and trauma groups revealed a significantly lower IL-1β level in the trauma group at 1 hour post-injury (p = 0.0228), followed by convergence at 6 hours (p = 0.3620). At 24 hours, trauma group levels exceeded those of sham animals significantly (p = 0.0157), while by 72 hours, the levels were again statistically indistinguishable (p = 0.6185), indicating resolution of the inflammatory response.

Table 1: Serum IL-1β levels by time point

Time Point	Sham (Mean ± SD) (Min- Max)	Trauma (Mean ± SD) (Min- Max)	p-value
1h	64.43 ± 13.28 (43.95-86.52)	49.03 ± 8.79 (33.59-60.34)	0.0228*
6h	44.87 ± 15.35 (20.76-74.98)	38.75 ± 7.71 (25.60-51.95)	0.3620
24h	46.26 ± 9.30 (35.58-61.81)	65.45 ± 13.22 (49.43-83.12)	0.0157*
72h	56.60 ± 12.24 (36.60-73.17)	53.68 ± 7.40 (43.02-62.70)	0.6185
Pairwise comparisons (p-value)	1h vs 6h: 0.0232* 1h vs 24h: 0.0211* 1h vs 72h: 0.3166 6h vs 24h: 0.8587 6h vs 72h: 0.1795 24h vs 72h: 0.1636	1h vs 6h: 0.0356* 1h vs 24h: 0.0161* 1h vs 72h: 0.3026 6h vs 24h: 0.0004* 6h vs 72h: 0.0024* 24h vs 72h: 0.0591	

**p-values indicate the statistical significance*

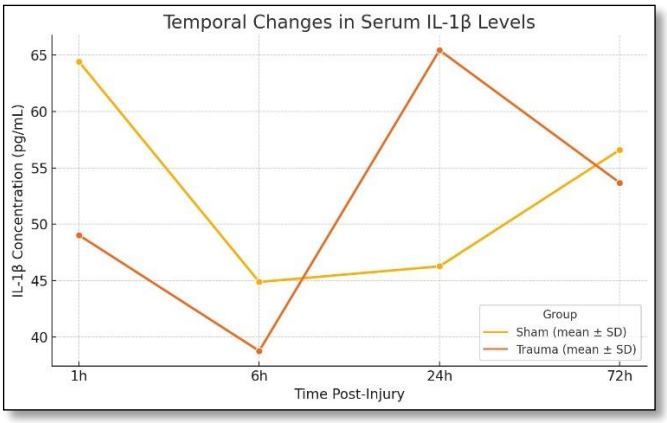

Figure 1: Temporal changes in serum IL-1β levels in sham and trauma group

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DISCUSSION

Traumatic brain injury is known to trigger a cascade of inflammatory events that play a critical role in secondary brain damage (1). IL-1β, a pivotal proinflammatory cytokine, is rapidly upregulated following injury and contributes to blood-brain barrier disruption, neuronal loss, and glial activation (3,4,15). This study aimed to elucidate the temporal expression profile of IL-1β in serum following experimental TBI in rats, offering insight into its potential as both a biomarker and a therapeutic target. Our findings demonstrated a dynamic pattern in the trauma group, marked by an initial decline, a peak at 24 hours, and a gradual decline by 72 hours. In contrast, sham animals showed a biphasic fluctuation, highlighting the importance of procedural controls.

The transient early elevation and observed biphasic IL-1β pattern in the sham group likely reflects the effects of anesthesia and procedural stress rather than true injury-related inflammatory responses. Previous studies have shown that commonly used anesthetics such as isoflurane or ketamine may modulate cytokine expression, including IL-1β, by dampening systemic immune responses (7). Moreover, nonspecific surgical handling and stress-induced neuroendocrine alterations may also contribute to cytokine fluctuations (16). In contrast, the trauma group exhibited an initial suppression of peripheral IL-1β likely related to early sequestration of cytokines at the site of injury and temporary microvascular leakage within the damaged brain tissue. Such findings emphasize the need to consider sham-related inflammation when interpreting cytokine-based biomarkers.

Our findings in the trauma group align with prior research demonstrating that IL-1β is rapidly induced in the central nervous system and periphery following TBI, with early IL-1β elevation within the first few hours and peak levels generally occurring between 4 and 24 hours depending on the injury model.

Notably, these studies have reported discrepancies in the timing and magnitude of IL-1β expression, which may result from differences in injury model (focal vs diffuse), species, severity, or tissue sampled (serum vs cortex vs cerebrospinal fluid)

Kinoshita et al. observed peak IL-1β mRNA and protein expression between 3 and 24 hours after fluid percussion injury in rats, while Lu et al. reported a surge in IL-1β concentrations at 6 hours using the weight-drop model (3,17). These temporal dynamics support the role of IL-1β as an early mediator of post-traumatic neuroinflammation. In addition, our study adds to this literature by focusing on serum levels at multiple defined time points, offering translational relevance for peripheral biomarker assessment.

Several mechanistic studies have confirmed that IL-1β plays a central role in secondary injury cascades following TBI, including disruption of the blood-brain barrier, microglial activation, excitotoxicity, and apoptotic signaling (8,15). Doğanyiğit et al. further highlighted IL-1β's upstream position in triggering inflammasome activation and amplifying the release of other pro-inflammatory cytokines such as TNF-α and IL-6 (15). Therapeutic inhibition of IL-1β via interleukin-1 receptor antagonist (IL-1Ra) or neutralizing antibodies has been shown to attenuate inflammation and reduce lesion volume in multiple preclinical TBI models (3,10). Therefore, IL-1β remains a promising target for anti-inflammatory treatment strategies.

Importantly, elevated IL-1β has been associated with worsened histopathological and behavioral outcomes (18). Multiple experimental studies have demonstrated that neutralization of IL-1β using interleukin-1 receptor antagonist (IL-1Ra) or monoclonal antibodies can significantly mitigate neuronal damage, reduce glial activation, and improve functional outcomes (19–21). Hellewell et al. showed reduced lesion volume and improved function with IL-1Ra treatment (20). Similarly, inhibition of the AMPK-SIRT1-NF-κB pathway, which regulates IL-1β, resulted in neuroprotection following TBI in the study by Zhang et al (22).

While many studies have focused on tissue levels of IL-1β in the brain, our study highlights the diagnostic value of peripheral (serum) IL-1β levels, which are more clinically accessible. Prior research has demonstrated that systemic IL-1β levels correlate with injury severity and prognosis in both animal models and human subjects (7,23). However, serum levels may also be influenced by extracranial factors, including systemic infection, extracranial trauma, or comorbid inflammation, which limit its specificity as a stand-alone biomarker (24).

Our results also diverged from some prior studies that reported a monotonic increase in IL-1β following TBI. For instance, in the study by Rothwell et al., IL-1β levels continued to rise for up to 72 hours in both serum and cerebrospinal fluid (21). These discrepancies may be attributed to variations in injury severity, anatomical localization, and differences in species or sampling protocols. Notably, the weight-drop model used in our study is known for its diffuse injury pattern, which may elicit different inflammatory kinetics compared to focal injury models such as controlled cortical impact (25).

From a translational perspective, understanding the temporal dynamics of IL-1β offers potential in refining clinical monitoring protocols and developing time-targeted anti-inflammatory therapies. Peak IL-1β expression at 24 hours post-injury may represent an optimal therapeutic window for IL-1β antagonism. Furthermore, IL-1β has been investigated in other neurological conditions including ischemic stroke and spontaneous intracerebral hemorrhage, where similar inflammatory cascades are activated (26,27). The utility of IL-1β as a biomarker may therefore extend beyond TBI and include a spectrum of acute brain injuries.

Future studies should expand on our findings by incorporating behavioral assessments such as the Morris water maze, rotarod, or open field tests to evaluate the functional impact of cytokine fluctuations (28,29). Correlation of IL-1β with histopathological outcomes—including neuronal loss, gliosis, and axonal injury—would also provide mechanistic insight. Moreover, longitudinal studies extending beyond 72 hours would help determine whether IL-1β levels resolve, persist, or oscillate in chronic phases. Comparative studies using different models—blast, evaluate the generalizability of our results (18,25,30).

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Nonetheless, several limitations must be acknowledged. First, the study is restricted to a 72-hour window and lacks histological or behavioral outcome assessments. Second, serum measurements may not fully reflect localized neuroinflammatory activity in brain parenchyma. Finally, the unexpected IL-1β fluctuations observed in sham animals indicate a need for improved procedural controls and possibly non-invasive cytokine sampling methods in future studies.

In conclusion, the present findings, together with previous experimental evidence, support the view that IL-1β exhibits an early localized and delayed systemic response after TBI, reflecting the complex dynamics of neuroinflammation. The observed elevation at 24 hours post-injury may represent a critical window for therapeutic intervention. IL-1β continues to hold promise as both a peripheral biomarker and a molecular target in TBI management, though it interpretation must be contextualized with experimental design, injury model, and time of sampling.

CONCLUSION

Our results underscore IL-1β's role as a sensitive and temporally regulated biomarker in the acute phase of TBI. The sharp elevation at 24 hours suggests a critical window for therapeutic interventions targeting IL-1β-mediated neuroinflammation. Furthermore, the return toward baseline by 72 hours may reflect the resolution phase of the systemic inflammatory response, though further studies are needed to assess long-term trends.

Future research should aim to correlate serum IL-1β levels with behavioral, cognitive, and histopathological outcomes to establish its prognostic value. Additionally, extended observation periods, comparative analyses with other TBI models, and parallel measurements in central nervous system tissue will be essential to fully elucidate the utility of IL-1β as a diagnostic and therapeutic target in neurotrauma.

Author contribution:
Working Concept/Design: OB, EU, HŞÇ
Data Collection: OB, İA, EC
Data Analysis /Interpretation: OB, SŞ, SBK
Text Draft: OB, EU, İA, SŞ, HSÇ, SBK, EC
Critical Review of Content: OB, İA, SŞ, SBK, EC
Final approval and accountability: OB, EU, İA, SŞ, HŞÇ, SBK, EC
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