wjpmr, 2022, 8(11), 09-13

SJIF Impact Factor: 5.922

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Research Article

ISSN 2455-3301

WJPMR

EFFECTS OF MIDAZOLAM ON CYTOKINE PRODUCTION IN THE BRAIN DURING BRAIN TUMOR RESECTION

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Article Received on 26/08/2022 **Article Revised on 15/09/2022** **Article Accepted on 05/10/2022**

ABSTRACT

Background: Cytokines produced in the brain cause worse outcome following traumatic brain injury. Effects of midazolam on cytokine in trauma or ischemic disease have been studied. We could expect midazolam could inhibit production of cytokines in the brain. This study investigated the effects of midazolam on cytokine production in the brain during brain tumor resection. **Methods:** Twelve patients for brain tumor resection using spinal drainage were divided into the Midazolam and Control groups. Anesthesia was maintained with isoflurane and nitrous oxide in oxygen. In the Midazolam group, midazolam was infused with 0.68 mg/kg/h for the first 15 min. followed by 0.25 mg/kg/h. IL-6, IL-8, and TNFα in the arterial blood, internal jugular vein and cerebrospinal fluid (CSF) were measured before surgery, after craniotomy, 2 hours in brain manipulation, and end of surgery. **Results:** IL-6 significantly increased in artery and jugular vein in both groups, but no significant differences were found between the groups. IL-6 in the CSF increased significantly at the end of surgery in both groups with significantly higher values in the Control group. In the CSF, IL-8 significantly increased in both groups with significantly higher values in the Control group at the end of surgery. TNFα significantly increased in artery, jugular vein and CSF with significantly higher values in the Control group after craniotomy. **Conclusions:** Continuous infusion of midazolam during brain tumor resection decreased production of IL-6 and IL-8 in the brain and TNFα in the brain and systemic circulation.

KEYWORDS: brain surgery, cytokine, midazolam.

INTRODUCTION

Interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor α (TNFα) are inflammatory cytokines. These cytokines are produced in the central nervous system (CNS).[1,2,3] Neuroinflammatory response contributes to increased intracranial pressure, cerebral edema, and neurological cell death following traumatic brain injury.[4] Effects of midazolam on cytokine in trauma or ischemic disease have already been studied. Midazolam inhibits production of IL-6 in human peripheral blood mononuclear cells.[5] Clinically, midazolam inhibited IL-6, IL-8 and TNFα production systemically.[6,7] Lei et al. showed that midazolam improved neuronal recovery after hypoxia and ischemia.[8] Therefore, we could expect that midazolam might inhibit production of IL-6, IL-8 and TNFα in the CNS. This study was performed to know the effects of midazolam on cytokine production in the brain when brain was damaged using human model of brain tumor resection.

MATERIALS AND METHODS

After the approval of the institutional review board and informed consent from patients, 12 patients scheduled for brain tumor resection using spinal drainage were divided into the Midazolam and Control groups. Anesthesia was induced with thiopental, sevoflurane and vecuronium. Maintenance of anesthesia was isoflurane and nitrous oxide in oxygen. In the Midazolam group, midazolam was infused with 0.68 mg/kg/h for the first 15 min. followed by 0.25 mg/kg/h. Isoflurane concentration was controlled to keep blood pressure within 20% of the control values. IL-6, IL-8, and TNFα in the arterial blood, internal jugular vein and spinal fluid (CSF) were measured before surgery, after craniotomy, 2 hours in brain manipulation, and end of surgery. IL-6 was measured with electro chemiluminescence immunoassay (ECLIA). IL-8 and TNFαwere measured with enzyme-linked immunosorbent assay (ELISA).

Data were shown as mean ± standard deviation. Statistical analysis was performed with the chi-square

test and factorial and repeated measures analysis of variance (ANOVA). A p value less then 0.05 was considered to be statistically significant.

RESULTS

No differences were observed in the background (Table 1).

Blood pressure significantly decreased after craniotomy and 2 hours in brain manipulation in the Control group, but no significant differences were observed between the groups (Fig.1).

Heart rate significantly increased at the end of surgery in both groups, but no significant differences were found between the groups (Fig.2).

IL-6 significantly increased after craniotomy, 2 hours in brain manipulation and at the end of surgery in artery in both groups, but no significant differences were found between the groups (Fig.3). In jugular vein, IL-6 increased significantly after craniotomy and at the end of surgery in the Control group and at the end of surgery in the Midazolam group without any significant intergroup differences (Fig.4). IL-6 in the CSF increased significantly at the end of surgery in both groups with significantly higher values in the Control group (Fig.5). IL-8 was not detected in the artery and jugular vein. In the CSF, IL-8 significantly increased at the end of surgery in the Control group and 2 hours in brain manipulation and at the end of surgery in the Midazolam group with significant higher value in the Control group than the Midazolam group at the end of surgery (Fig.6). TNFα significantly increased after craniotomy in both groups in artery with significantly higher values in the Control group than the Midazolam group (Fig.7). TNFα in jugular vein significantly increased after craniotomy in the Control group and after craniotomy and 2 hours in brain manipulation in the Midazolam group with significant higher values in the Control group after craniotomy (Fig. 8).

Table 1: Background of the patients.

	Midazolam group	Control group
Age (years)	56 ± 7	52 ± 8
Male/Female	4/2	3/3
Body weight (kg)	58 ± 7	58 ± 8
Height (cm)	160 ± 6	158 ± 5
Consumption of Isoflurane (mL)	135 ± 40	149 ± 62
Astrocytoma/Glioblastoma	3/3	2/4
Duration of surgery (min)	471 ± 60	478 ± 49

Mean ± SD

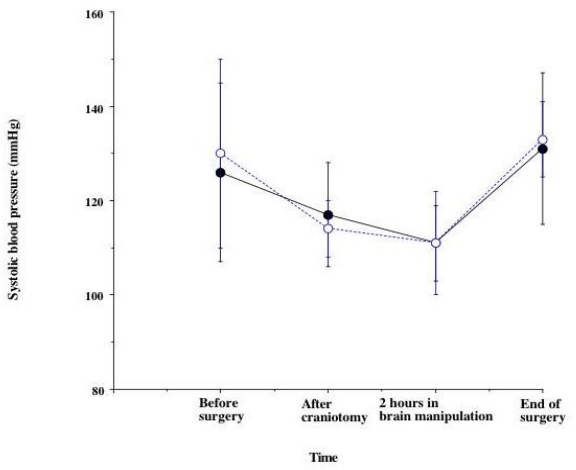

Figure 1: Systolic blood pressure.

Closed circle, Midazolam group; Open circle, Control group; Bars show standard deviation.

*: P < 0.05 vs. the value before surgery

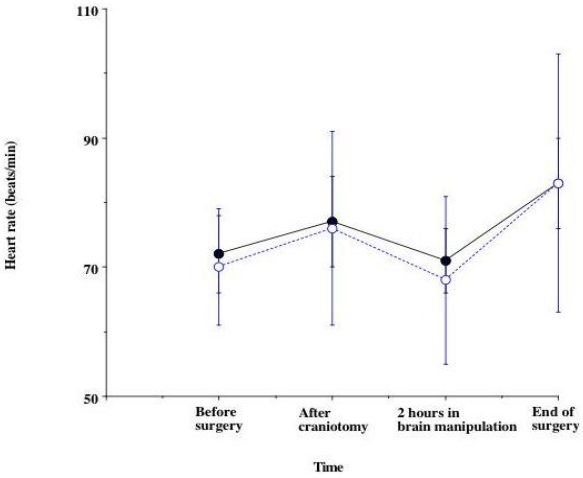

Figure 2: Heart rate.

Closed circle, Midazolam group; Open circle, Control group; Bars show standard deviation.

*: P < 0.05 vs. the value before surgery

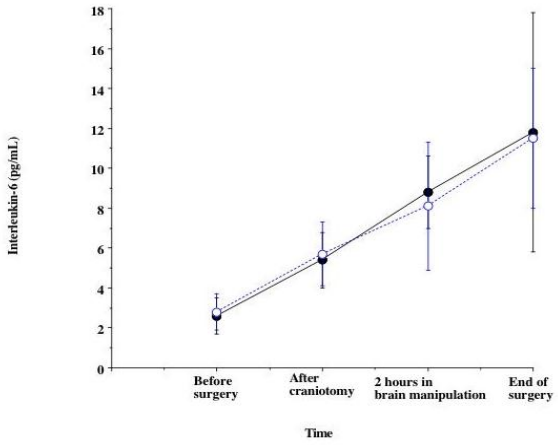

Figure 3: Interleukin-6 in artery.
Closed circle, Midazolam group; Open circle, Control group; Bars show standard deviation.

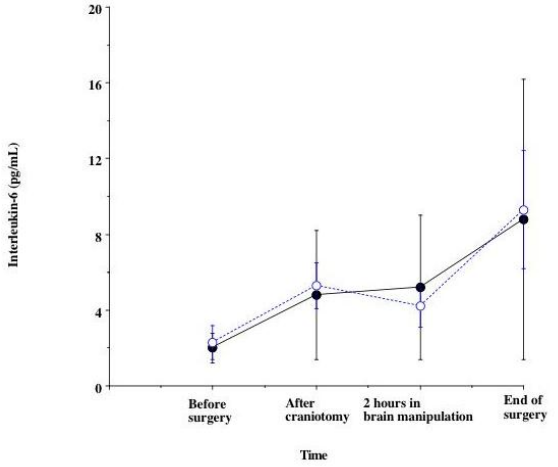

Figure 4: Interleukin-6 in jugular vein.
Closed circle, Midazolam group; Open circle, Control group; Bars show standard deviation.

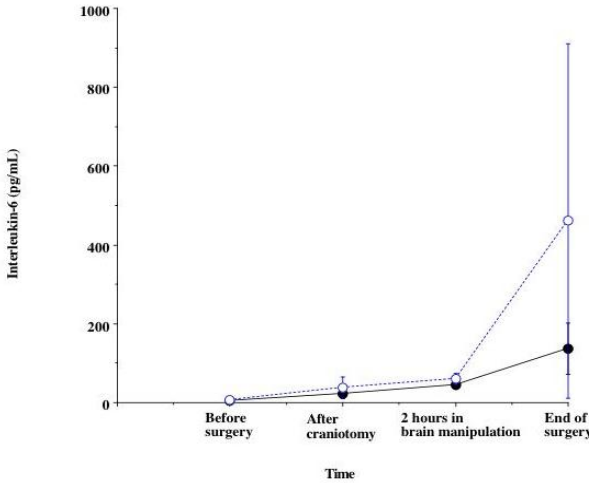

Figure 5: interleukin-6 in spinal fluid.
Closed circle, Midazolam group; Open circle, Control group; Bars show standard deviation.

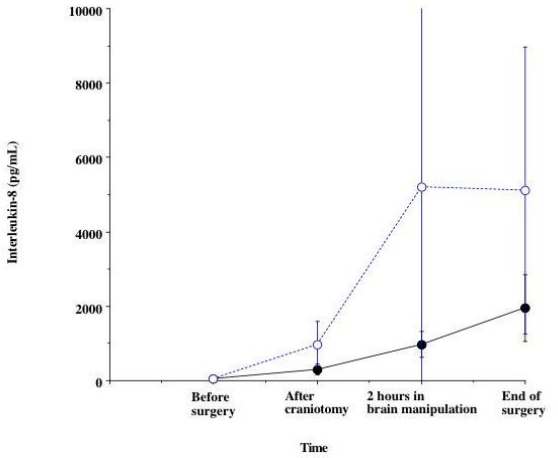

Figure 6: Interleukin-8 in spinal fluid.
Closed circle, Midazolam group; Open circle, Control group; Bars show standard deviation.

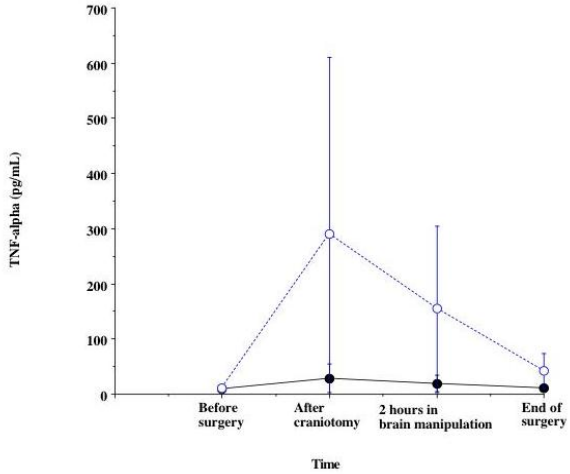

Figure 7: TNFα in artery.
Closed circle, Midazolam group; Open circle, Control group; Bars show standard deviation.

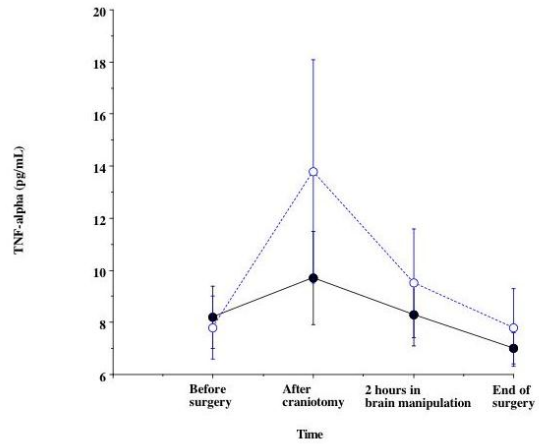

Figure 8: TNFα in jugular vein.
Closed circle, Midazolam group; Open circle, Control group; Bars show standard deviation.

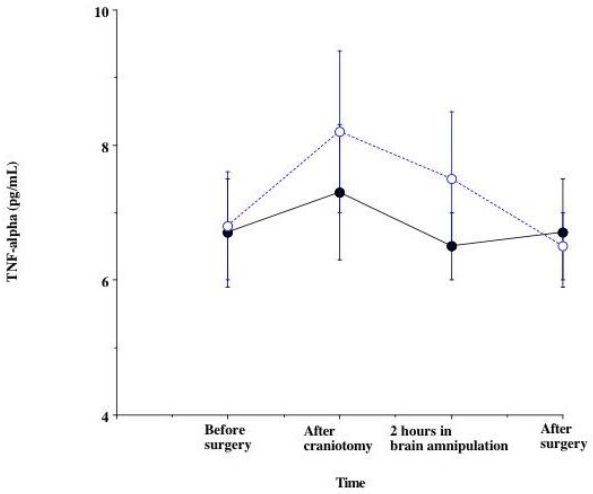

Figure 9: TNFα in spinal fluid.
Closed circle, Midazolam group; Open circle, Control group; Bars show standard deviation.

DISCUSSION

Our results showed that continuous infusion of midazolam during brain tumor resection decreased production of IL-6 and IL-8 in the brain and TNFα in the brain and systemic circulation.

Astrocytes produce IL-6 in response to stimulation by proinflammatory cytokines such as TNFα.[1] IL-8 is produced in astrocytoma and glioblastoma, most likely by tumor cells, and possibly by tumor-infiltrating macrophages or microglial cells.[3] Glial cell lines produce TNFα.[9] Therefore, increases in these cytokines in this study might be induced by surgical inflammation and tumor cells. Elevated serum IL-6 increases the permeability of the blood-brain barrier. Increased IL-6 and TNF-α in the CNS is considered to induce damage to astrocytes and oligodendrocytes and trigger apoptosis of neuronal cells.[10] IL-8 promotes neutrophil-endothelial adhesion and recruits neutrophils by forming a chemotactic gradient.[11] In the presence of inflammatory leukocytes, IL-8 increases vascular permeability.[12] IL-8 stimulates chemotaxis, changes in morphology, adhesion, diapedesis and release of lysosomal enzymes.[13] IL-8 may also mediate cytotoxicity by promoting release of proteases and oxidant species from neutrophils in injured brain.[14] TNFα enhances cytotoxic T-lymphocyte development, and looses capillary endothelial junctions to cause leakage of water and plasma proteins into tissues.[9] The initial TNF-α in CSF and serum may reflect the early neurological severity and functional disability in stroke patients as well as have a predictive value for the outcome of stroke.[15] Higher levels of these cytokines in the CSF induce cerebral vascular contraction and poor prognosis.[16,17] Therefore, inhibition of these cytokine responses might induce good outcome after brain injury.

Peripheral-type benzodiazepine receptor expression levels are low in normal human brain, but their levels increase in inflammation, brain injury, neurodegenerative states and gliomas.[18] Midazolam suppressed IL-1β induced release of IL-6 in rat glioma cells,[7] and it also suppressed lipopolysaccharide induced release of TNFα in rat microglial cells via peripheral benzodiazepine receptors.[19] Midazolam decreased release of IL-8 from lipopolysaccharide stimulated neutrophils.[20] Midazolam induced marked and delayed inhibition of the lipopolysaccharide-induced production of TNFαand IL-6 by monocytes isolated from peripheral blood.[21] There are some clinical studies to show the effects of midazolam on the production of systemic cytokines. Long-term sedation with midazolam inhibited IL-6 production in surgical intensive care unit patients. [6] Continuous infusion of midazolam decreased IL-1β, IL-8 and TNFα in pediatric patients after surgery.[7] Midazolam decreased production of IL-6, IL-8, and TNFα in critically ill surgical patients.[6] However, we could not find any clinical studies to show the effects of midazolam on cytokine production in the brain. Brain injury has a lot of variations such as severity of injury, time from onset to hospitalization, therefore, we chose surgery for brain tumor to keep within a narrow range of the onset and severity of brain injury in this study. The present results suggested that midazolam could decrease brain damage and might improve outcome in brain injury due to suppression of the production of IL-6, IL-8, and TNFα.

CONCLUSIONS

The results of this study showed that midazolam decreased production of IL-6 and IL-8 in the brain and TNFα in the brain and systemic circulation in brain tumor resection.

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