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Original Article

The effects of sodium-2-mercaptoethanesulfonate application on the neural and neurovascular tissues: An experimental animal study

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Abstract

Background: Sodium-2-mercaptoethanesulfonate (MESNA) is a protective agent that is also used as "a chemical dissector" in various surgical fields. The aim of this study is to evaluate the toxic effects of MESNA on neural and neurovascular structures based on a morphological analysis and examine its safety in neurotological applications.

Methods: Three groups of guinea pigs were used as subjects. MESNA solution (50 and 100%) and saline solution were applied to the subarachnoid space over the brain tissue via a middle fossa approach of study and control groups, respectively. Effects of MESNA were assessed by means of light microscope. McNemar Chi-square test was used to evaluate the histopathological findings. Statistical significance of $P < 0.05$ was taken as criterion.

Results: No morphological changes were observed on vascular and neural structures in the study groups in both concentrations, compared to the control group.

Conclusions: On a morphological basis, a single application of MESNA does not cause any morphological changes that indicate a toxicity in neural and neurovascular structures.

KeyWords: Neurotologic surgery, neurotoxicity, sodium-2-mercaptoethanolsulfonate

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INTRODUCTION

Sodium-2-mercaptoethanesulfonate (MESNA) is the sodium salt of 2-thiosulfonate anion which is the coenzyme in methanogenesis by anaerobic archaebacteria.[8] MESNA has a widespread usage in medicine due to its protective, antioxidant and mucolytic features.[1,3,5,7,13]

As a mucolytic agent, it disrupts disulfide bonds of the mucous polypeptide chains. This feature is used in respiratory medicine (in the treatment of chronic bronchitis, asthma, chronic pharyngolaryngitis, etc.) and also in some surgical treatments.[1]

By the agency of the knowledge that the physiologic and pathologic adhesions between different layers are rich in disulfide bonds, MESNA has gained attention in recent years as "a promising chemical dissector" in neurotologic

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surgery to provide a cleavage between tumor and important structures of nervous system such as cranial nerves, brain, cerebellum, brainstem, arteries, and veins.[14] Although tolerability and toxicity of MESNA have been established in various trials, the effects on the neural and neurovascular tissues are not evident. We aimed to determine the local effects of MESNA on neurovascular and neural tissues by morphological analysis.

MATERIALS AND METHODS

Animals

Fifteen healthy adult male albino guinea pigs were used in this study. Subjects were acclimatized to laboratory conditions for 7 days at animal experiments laboratory. All animal handling was done as prescribed by Declaration of Helsinki and in compliance with Gazi University Animal Experiments Local Ethics Committee regulations (GU-ET 13.056). Subjects were divided into three groups. Fifty percent MESNA was applied to six guinea pigs in study-1 group. In study-2 group, also six subjects were applied 100% MESNA. And three subjects were applied saline only as the control group.

Anesthesia

The animals were anesthetized by 2% of the compound solution of 5 mg/kg xylazine (Rompun®, Bayer Vital, Leverkusen, Germany) and 35 mg/kg ketamin HCl (Ketalar®, Eczacibasi Warner Lambert, Istanbul, Turkey) intramuscular injection.

Surgery

Surgery was performed under a surgical microscope and sterile conditions. A supraauricular 2 cm incision was performed on the left side for all subjects [Figure 1]. Zygomatic root was exposed and a 1 cm diameter circle craniotomy was made 0.5 cm above the root with a diamond burr [Figures 2 and 3].

After the dura was opened as a flap, cerebrospinal fluid was released. Penrose drain was put to avoid the injury to the brain tissue and 1–2 cc injection (study-1 group: 50% MESNA and 50% saline compound, study-2 group: 100% MESNA, control group: Saline) was done over the Penrose to the subarachnoid space and waited with 45° elevation of the head for 5 min to delay the escape of the fluid [Figures 3 and 4]. The craniotomy area was closed with bone wax and the surgical wound was sutured. The guinea pigs were sacrificed on day 7 by intracardiac blood collection under deep anesthesia.

Evaluation of the materials

Following the sacrification, the brain tissues were harvested and prepared according to hematoxylin-eosin staining protocol. The microscopic evaluation was carried out to detect whether the following were present in the samples:

- Neurons: Loss, nuclear or cytoplasmic inclusions, evidence of ischemia, loss of normal cytoplasmic volume and organelles such as endoplasmic reticulum, intactness of the nuclear structure, and the presence of nucleoli
- Astrocytes: Increased number, gemistocytic transformation, evidence of gliosis, nuclear or cytoplasmic enlargement or inclusions
- Oligodendrogliocytes: Increased number
- Microglial cells: Presence or predominance of these cells, presence of microglial islands or nodules
- Blood vessels: Hyperplasia or hypertrophy, evidence of endothelial proliferation, hemorrhage
- Leptomeningeal tissue: Disruption of the natural lining of these cells, alterations in the blood vessels therein
- Inflammatory reaction: Presence of lymphocytes, neutrophils, edema.

RESULTS

The observation of the morphological features of brain tissues revealed no alterations in vascular and neural structures with both concentrations of MESNA [Figures 5-10].

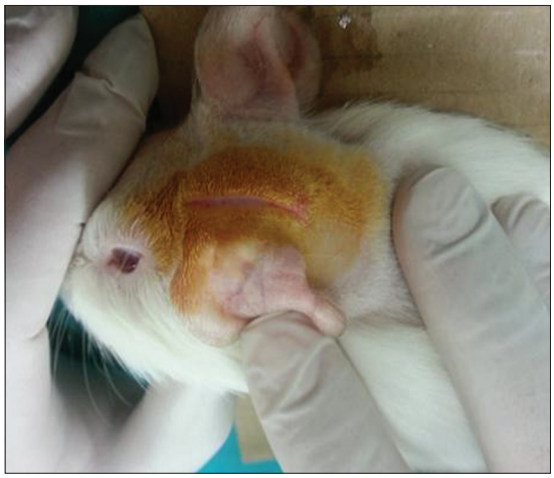

Figure 1: Surgical procedure; skin incision for the procedure

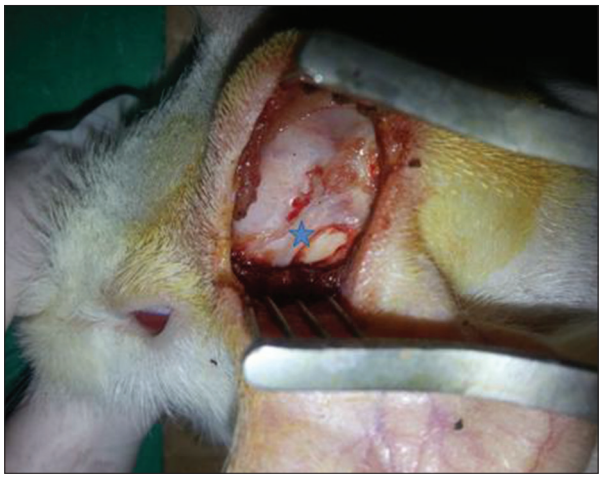

Figure 2: Surgical procedure; exposure of the zygomatic root (star)

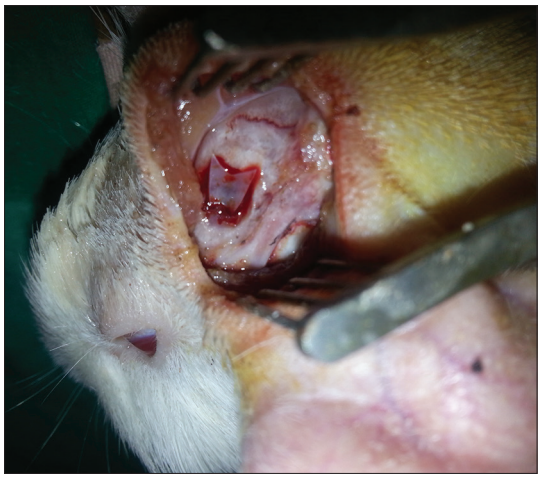

Figure 3: Surgical procedure; craniotomy above the zygomatic root, dura flap with the Penrose drain

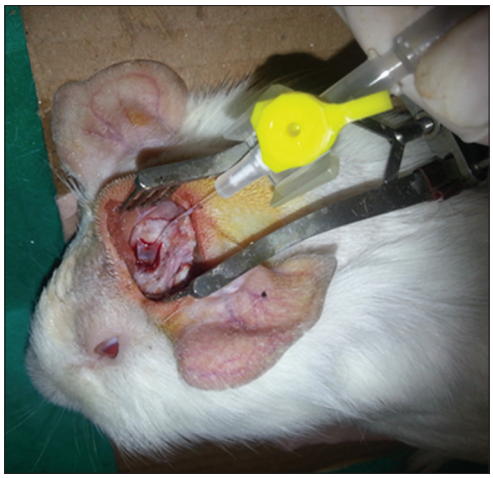

Figure 4: Surgical procedure; injection to the subarachnoid space

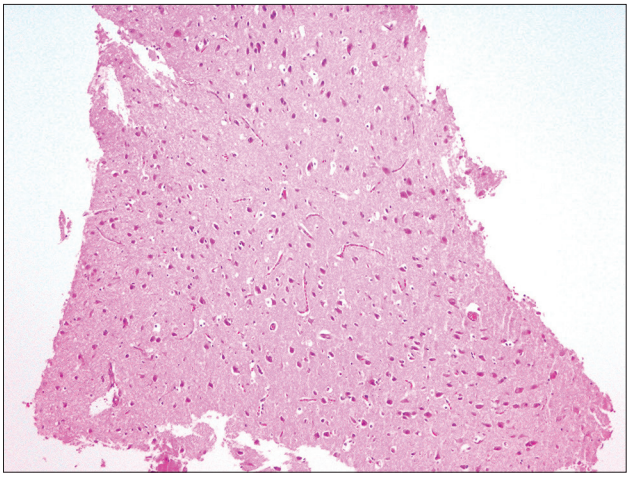

Figure 5: Histologic section of study-1 group (H and E, ×10). No morphological change was seen in each group

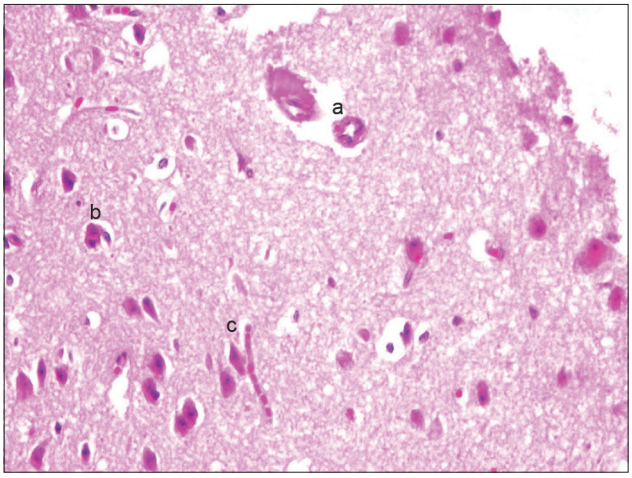

Figure 6: Histologic section of study-1 group (H and E, ×40). No morphological change of arteriole and venule (a), neuron (b), capillary (c) was seen in each group

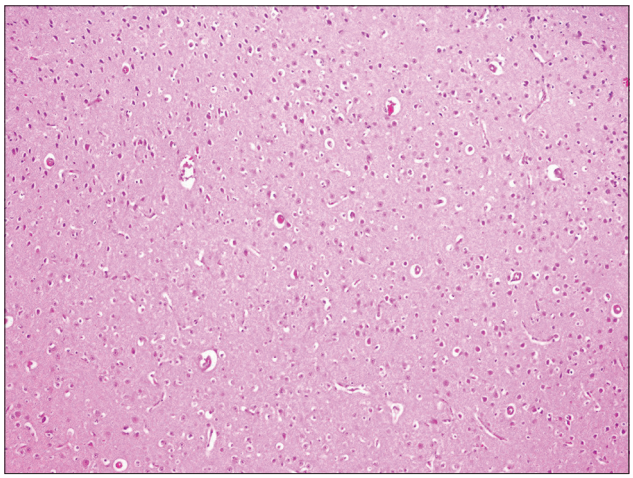

Figure 7: Histologic section of study-2 group (H and E, ×10). No morphological change was seen in each group

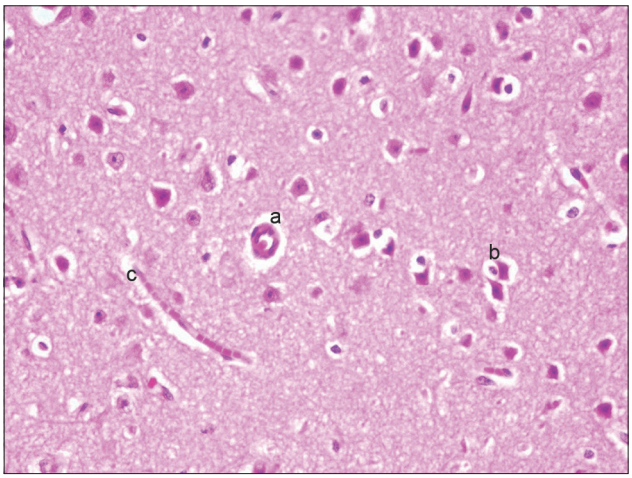

Figure 8: Histologic section of study-2 group (H and E, ×40). No morphological change of arteriole and venule (a), neuron (b), capillary (c) was seen in each group

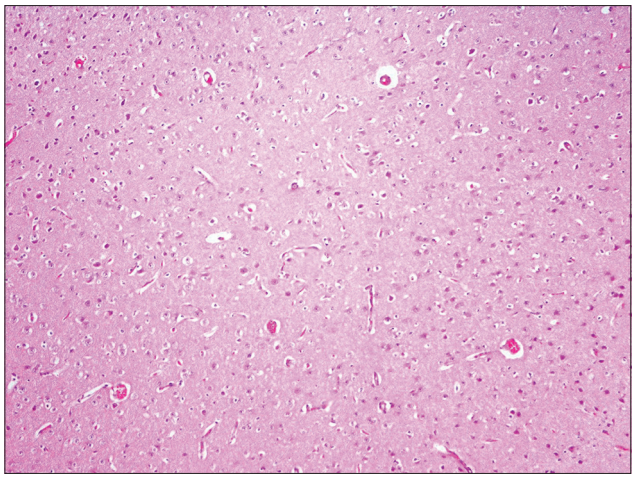

Figure 9: Histologic section of control group (H and E, ×10). No morphological change was seen in each group

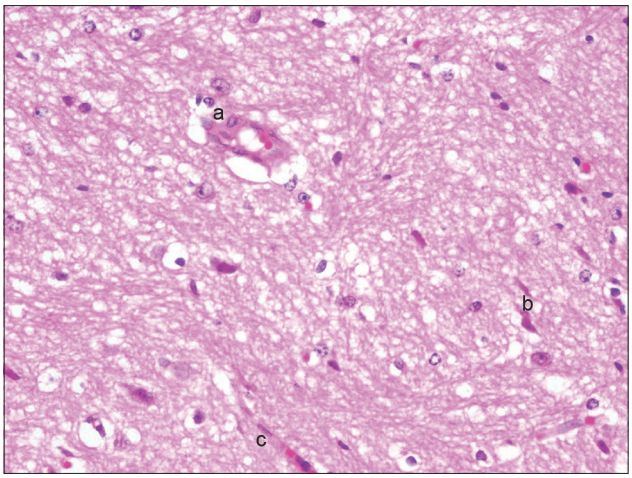

Figure 10: Histologic section of control group (H and E, ×40). No morphological change of arteriole and venule (a), neuron (b), capillary (c) was seen in each group

DISCUSSION

Treatment of neural tissue pathologies is a challenging issue because of the high morbidity and mortality rates. In otoneurosurgery, the objective is total tumor extirpation without any life-threatening complication or a loss in quality of life due to inhibitory sequelae. During mechanical dissection of the tumor, brain manipulation can lead to cerebral/cerebellar edema, subdural hematoma or acute brain dysfunction. Cerebrovascular complications, such as carotid artery rupture due to excessive adventitial dissection are also of major concern of the operation. Cranial nerve deficits have an impact on postoperative quality of life and are also potentially life-threatening problems.[4] Ease of tumor extirpation and prevention of complications with "a chemical dissector" can reduce morbidity, mortality, and shorten the duration of the operation compared with the mechanical dissection.

MESNA has been used locally (by irrigation or surgical sponges) in otologic surgery for several years, especially in cases with adhesive otitis media to elevate the adhesive tympanic membrane by intratympanic usage[12] and in chronic otitis media with cholesteatoma to dissect cholesteatoma matrix from underlying tissues of great interest, such as sigmoid sinus and facial nerve by irrigation especially when a dehiscence is present. MESNA has a lysing effect on adhesions between different layers by disrupting disulfide bonds. Previous experiences with MESNA in otologic surgery prompted us to use it in neurotologic surgical procedures, such as acoustic neuromas, glomus tumors, meningiomas, and tumors of the skull base.

As for neurotoxicity, repeated intraperitoneal injection of high dose MESNA (>300 mg/kg) induced spinal activity and contralateral activity of the trigeminoreticular areas of the brainstem-spinal cord junction in rat models.[6] However, the planned dose of the application in neurotologic surgery is not that high and former animal studies suggest the neuroprotective feature of systemic MESNA application.[2,11] A single dose of 150 mg/kg MESNA was shown to decrease the apoptotic activity (caspase-3 activity) in the spinal cord following ischemia/reperfusion injury in a rabbit model.[2] In another study, MESNA increased the levels of the antioxidant enzymes (glutathione peroxidase and superoxide dismutase), decreased oxidative enzymes and molecules (nitric oxide, nitric oxide synthetase, and xanthine oxidase) and protected the brain tissue histopathologically with systemic administration immediately after the brain injury in rat models.[11] These studies showed the neuroprotective effect of MESNA by enzyme systems as a systemic one dose regimen (150 mg/kg) with a short exposure interval (24 h). In guinea pig models, the otologic effects of 10 or 20% of MESNA application locally to the middle ear were analyzed, no toxic effect of MESNA was seen on cochlear morphology or inner ear. These studies indicate that MESNA is not an ototoxic agent at least in a morphologic and structural manner. In accordance with the neurologic origin of the inner ear, the nonototoxic agent can also be thought as nonneurotoxic.[9,10] In addition, the absence of histological changes of the neural and neurovascular tissues in our study, supports previous studies indicating MESNA as a nontoxic agent.

Consequently, we predict MESNA as a promising chemical dissector which can be used in neurootologic surgery. But still further information is needed to assess its safety as there are some limitations in our study and also in the former studies. The most important limitation is the method of neural and neurovascular damage assessment. Our study based on morphological

analysis of the neural and neurovascular structures after the application of MESNA. Functional neurological assessment, which is the gold standard evaluation method of the neural function is still lacking.

A reduction in morbidity and mortality can be expected by a chemical dissector due to avoiding mechanical trauma to neural and neurovascular tissues during neurootological surgery. However, it is not probable to inform this data as this is a preliminary animal study, comparative trial in humans is still needed. Further studies must interest in neurophysiological assessments in animals and human safety trials.

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Conflicts of interest
There are no conflicts of interest.

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