Eur J Transl Myol 33 (1) 10778, 2023 doi: 10.4081/ejtm.2023.10778

Epidural and subdural hematoma following spinal anesthesia in infants rat model

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Abstract

The aim of this study was to assess the epidural and subdural hematoma following spinal anesthesia in infants' rat model. We investigated during 10, 15, and 20 days' rats in group 1: intrathecal injection of bupivacaine 3.75 mg/kg (n = 7); group 2: received 37.5 µl midazolam 0.1% intrathecal with 37.5µl fentanyl 0.005% (no=7); injected into group 3 methylene blue 1 mg/ml (No. 7). Rats were exposed to spinal anesthesia in infancy and rotarod in motor function in adulthood. Histological evaluation and tissue extraction were also performed after the treatment and magnetic resonance imaging (MRI) of the head. MRI of the head of all rat pups that showed similar symptoms were performed. 4 rat pups showed the symptoms of hematoma Group1: small acute subdural hematoma at the left posterior temporal-parietal junction (PTPJ) and group 2 (one: right temporal epidural hematoma, two: Small acute subdural hematoma in the right temporomandibular area, and three: frontal-temporal-parietal-occipital hematoma). the rat pup that had epidural hematoma died 6 hours later. Finally, in the first group, one rat and the second group three rats showed hematoma symptoms. For these three rats, a histopathologic study was performed and indicate the presence of small acute subdural hematoma at the left posterior temporal-parietal junction, right temporal epidural hematoma, and frontal-temporal-parietal-occipital hematoma. In summary, because subdural or epidural hematoma of the skull can have serious consequences, differential diagnosis is very important for pain after spinal anesthesia.

Key Words: Spinal anaesthesia; subdural and epidural hematoma; postdural puncture headache; infant rats.

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Epidural and subdural hematomas are common in trauma of skul and in brain injuries.[1] In the epidural, bleeding occurs between the skull and the dura, while in the subdural there is bleeding between the dura and the arachnoid membrane.[2] Subdural hematoma (SDH) is the blood that is inside the skull but it has accumulated outside the brain under the hard outer covering of the brain called the dura. This lesion is one of the most common intracranial mass lesions and is seen in both people with head injuries and those with less injury, such as the elderly or those taking anticoagulants.[3] A subdural hematoma occurs either spontaneously or aftet an operation such as a lumbar puncture.[4] Even with the best medical care, complications and mortality of this lesion are high. The size, location, and duration influence the clinical effects of a subdural hematoma.[5] When the etiology is unknown, the time of hematoma occurrence is determined by its appearance. These cases and the patient's neurological and medical condition determine the treatment process and affect the outcome.[6] In general, when subdural hematomas are acute, they last less than 72 hours and are dense on computed tomography scans.[7] The sub-acute stage usually starts 3 to 7 days after the acute damage. chronic subdural hematoma develops during several weeks and the brain is less dense.[8] The manifestations in critical subdural hematoma are very different. Although many patients with this lesion are in coma at the time of admission, approximately 50% of people with head

injuries are classified as moderately or mildly injured.[9] Skull fracture due to blunt trauma leads to rupture of the middle meningeal arteries. Fractures usually occur more in the temporal bone area, and unlike subdural hematoma, the fracture requires a great deal of force.[10] In children, because their skulls are more deformable, temporary displacement of the skull bones can lead to rupture of blood vessels without causing a skull fracture. Because the bleeding is under arterial pressure, the hematoma may spread rapidly.[11] Rapid drainage is almost always necessary. The biggest current challenge for children under anesthesia is the dangerous effects of general anesthesia on their brains.[12] Anesthetic agent appears to be the most damaging lesions of the cranial mass and occurs when exposed to a rapid period of synaptogenesis. The peak of synaptogenesis in rats lasts nearly from birth to day 10 and peaks on day 7 in the cerebral cortex.[13] In humans, this is roughly the period from the third trimester of pregnancy to the first 3 years of life.[14] In mice and rats, brain growth is faster in the first 2 weeks of life after delivery. The state of brain maturation in 7-day-old mice after birth is comparable to that of 7-day-old mice and is consistent with premature human neonates. On the other hand, the most common problem in performing spinal anesthesia is a headache.[15] The response of postoperative Dural headache (PDPH) to increased fluid intake and bed rest is about 48 hours. Long PDPH occurs either due to epidural or subdural hematoma,[1-4] or due to intracerebral hemorrhage. These neurological complications occur after an accidental or intentional dural puncture. Although serious side effects from this anesthesia approach are rare, they can be devastating.[16] The incidence of hematomas is estimated to be about 1: 150,000 for epidural blocks and 1: 22,000 for spinal anesthetics. The lesion is more catastrophic if there was no permanent neurological disorders, spinal hematoma may not be considered.[17] Some of the factors involved in increasing the incidence of this lesion include gender of woman, aging, placement of traumatic needle catheter, placement of a static epidural catheter, and immediate administration of preoperative, intraoperative, and postoperative low molecular weight heparin (LMWH).[18] There is usually an abrupt onset of severe pain in the back and legs with numbness, weakness, bladder and bowel dysfunction. If a patient is suspected of having a spinal hematoma, neuroimaging (MRI and CT scan) and neurological consultation should be performed instantly. There is usually an improvement in patients who undergo decompression surgery in between 8-12 hours.[19] Studies in models of infant rats have shown that exposure to several sedative-hypnotic drugs, such as benzodiazepines, n-methyl-d-aspartate receptor antagonists, and inhaled anesthetics, causes significant nerve damage, and bleeding disorders, especially at 10 days postpartum age.[20,21] Thus, the aim of this study was s to establish a rat model of epidural and subdural hematomas to study effects of different anesthetic procedures

Materials and Methods

This study was approved by the Ethics Committee of the Zabol University of Medical Sciences, Zabol, Iran. Groups of rats were housed in a room with a 12-hour light and dark cycle and easy access to water. They were kept in cages with their littermates and mothers and then with their littermates until weaning at the age of 25 days. The experiments were performed in an acrylic container in which the temperature was controlled at 36.8° C. Direct core temperature was not performed, but the core body temperature was set between 36.5 and 37.5 ° C.[22]

Puppies were examined regularly by researchers. P10 and P15 rats were separated from their mothers for spinal injections and behavioral tests and then they were quickly returned for heat and lactation. P20 rats were allowed access to water and food at all times except for spinal injection and behavioral testing. Rats were randomly divided into different groups based on age. Group 1: received intrathecal injections of Bupivacaine 3.75 mg/kg (No=7); Group 2: received combines of intrathecal 37.5µL midazolam 0.1% and 37.5 µL fentanyl 0.005% (No=7), and Group 3: Methylene Blue Injections 1 mg/ml (No=7). Pilot experiments were performed to evaluate the spread of injections in the subarachnoid space of the spine. Then mice were injected with 1 mg/ml methylene blue solution. Then, the development of methylene blue in the autopsy of these animals were examined 10 minutes after intrathecal injection.[18] Thermal pain obstruction was assessed using a hot plate test. The hind paws (left then right) were exposed to a hot plate (Model 39D Hot Plate Analyzer; IITC Inc., Woodland Hills, CA) at 52 ° C for infants P10 and P15 and 56 °C for adolescents P20, respectively. The time (thermal exit delay) was measured with a stopwatch until the rats raised their paws. After 12 seconds, the paw tested was removed to prevent injury to the animla or to cause hyperalgesia. Thermal withdrawal delay was measured every 10 minutes for at least 40 minutes after intrathecal injection until complete recovery. Pain relief was performed by removing the hind paw to von Frey filaments. A set of strings was applied with increasing flexural force and the force in grams was recorded from the filament that first triggered the exit reaction. The mechanical withdrawal threshold was initially recorded every 10 minutes for at least 40 minutes.

Histological assessment and tissue extraction for the last three rats were sacrificed after the treatment and Magnetic resonance imaging of the head. Rats were washed with 0.9% NaCl and then killed.[21] During dissection, the brain tissue of the skull (except the basal region) was removed. To determine the level and extent of the hematoma, imaging was performed using a high-resolution camera. Along a 3 mm artificial line behind

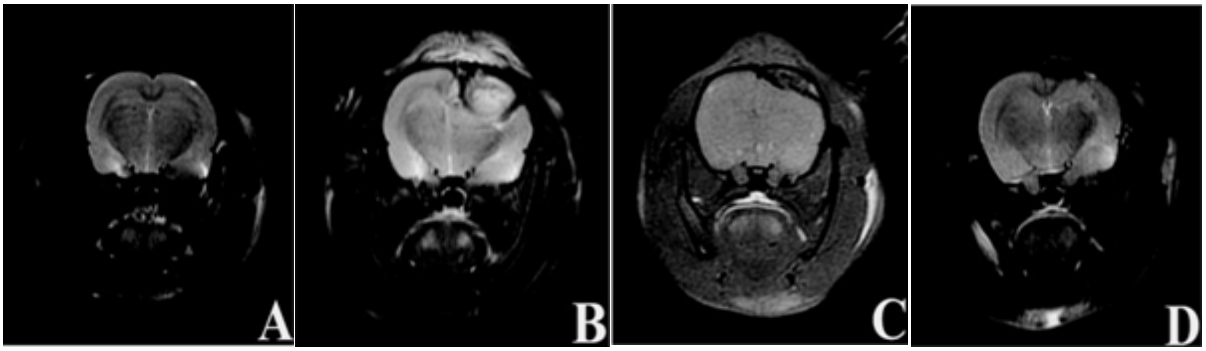

Fig 1. *Magnetic resonance imaging of the head of 4 rat pups:* ***A:*** *Group1: Small acute subdural hematoma at the left posterior temporal--parietal junction received Intrathecal Injections of Bupivacaine 3.75 mg/kg;* ***B:*** *Group 2 Rat number one: right temporal epidural hematoma (EDH) received intrathecal 37.5 µL midazolam 0.1 %, plus 37.5 µL fentanyl 0.005%;* ***C****: Rat number two: small acute subdural haematoma in the right temporo-occipital region, Methylene Blue Injections 1 mg/ml;* ***D:*** *Rat number three: frontal-temporal-parietal-occipital hematoma.*

the hole, the whole brain, including the base bone, was divided into two approximately equal parts. The initial stages of tissue extraction were the same for all evaluations.[2] For staining of hematoxylin and eosin (H&E), first, since it was necessary to preserve the intact Dura, the Dura was fixed at room temperature for 48 hours by inserting 3 styles of 25G needles into the cortex before immersing the brain in 4% paraformaldehyde. The brain was then cut into 10 mm units. Then, the unit was dewatered with graded ethanol and purified in dimethyl benzene and then embedded in paraffin. The 10 mm coronary unit was then cut into 0.5 mm sections in which H&E staining was performed according to standard methods.

Results

Infant rats recovered fully and returned to normal conditions 8 hours after spinal anesthesia and thermal and mechanical tests. They returned and settled in room with a 12-hours light/dark cycle. Rat pups were kept in cages with their mothers and cubs. After 5 days of the experimental procedures, 3 rats in the first group and 4 rats in the second group had symptoms such as confusion, severe imbalance, behavioral changes, vomiting, severe sleepiness, weakness, lethargy, and eventually seizure. When they started to vomit, intracranial lesions were suspected. In clinical and biochemical analyzes, hemoglobin, total and differential

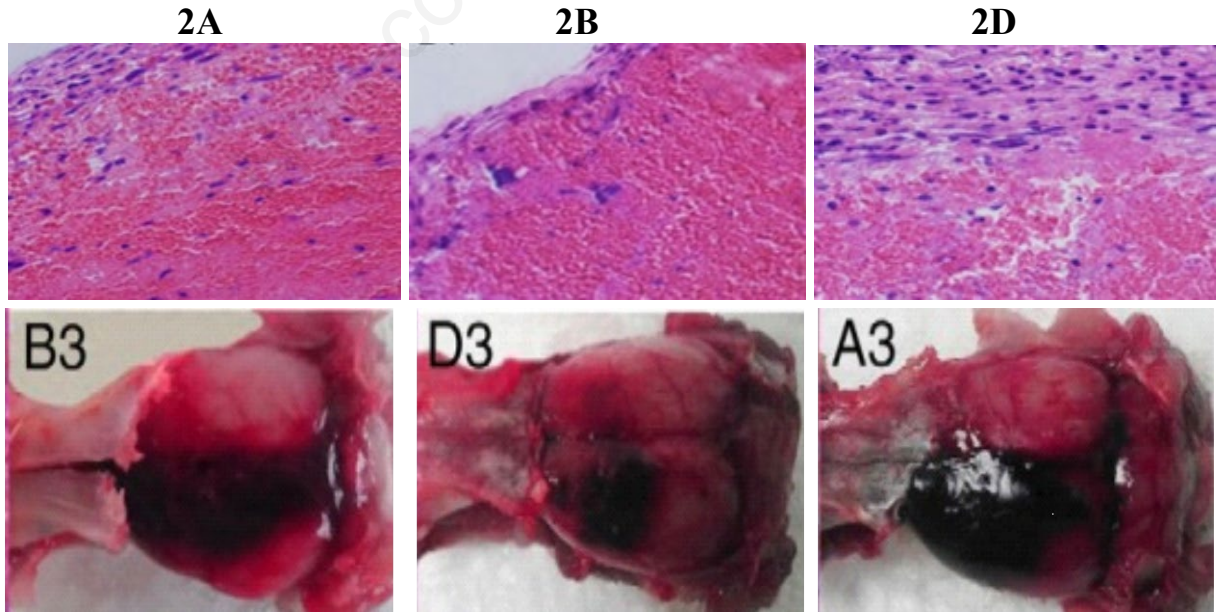

Fig 2. Presence of small acute subdural hematoma at left posterior temporal-parietal junction (2A), right temporal epidural (2B) and frontal-temporal-parietal-occipital (2D) locations. Gross pathology in B3, D3, A3.

leukocyte count, platelet count, bleeding time, clotting time, prothrombin time, and active partial thromboplastin time (APTT) were normal. Liver and kidney function tests were also normal. Magnetic resonance imaging of the head of one of the puppies (Group 2) showed a small acute subdural hematoma in the right temporal posterior without mass effect. The rat pup was quarantined in a quiet environment, fully recovered and was discharged after 5 hours. Magnetic resonance imaging of the head of all six other rat pups showing similar symptoms was performed. Finally, in 3 other rat pups (1 in the first group) and (2 in the second group), they also showed the symptoms of hematoma (Group1: small acute subdural hematoma at the left posterior temporal--parietal junction (PTPJ) (Figure 1: A), and group 2(rat number one: right temporal epidural hematoma (EDH) (Figure 1: B), rat number two: small acute subdural hematoma in the right temporo-occipital region (Figure 1: C), and rat number three: frontal-temporal-parietal-occipital hematoma) (Figure 1: D), the rat pup that had epidural hematoma died 6 hours later. Finally, in the first group, one rat and the second group three rats showed hematoma symptoms. For these three rats, a histopathologic study was performed according to the description given in the materials and methods. The histopathologic study of the brain tissue indicated the presence of a small acute subdural hematoma at the left posterior temporal-parietal junction (Figure 2: A), and right temporal epidural hematoma.

Discussion

Spinal anesthesia by mean of a Dural puncture can be associated with pain and even cerebral hemorrhage. Pain is one of the most common complications after lumbar puncture and usually occurs in ≤40% of cases. Such pains are probably due to excessive leakage (250 ml per day -1)[7] of cerebrospinal fluid (CSF) through the Dural foramen, which causes the displacement of the tail structures inside the skull. This transfer trough the dura of CSF inside the pain-sensitive skull stretches the sinuses and blood vessels and causes pain. Normal postdural puncture headache (PDPH) may occur immediately after spinal anesthesia and resolves within a few days.[21] Recently, Soliman et al. reported that 17 patients with intracranial hemorrhage had pain for more than 5 days after myelography.[22] Other researchers have stated that subdural hematoma pain was more severe than PDPH and was also persistent when lying down.[23,24] PDPH was the most common complication of using large traditional Quincke Spinal Needles. Its incidence is minimized by using 29G11 needles and pencil tip needles.[12] Epidural blood patches have been reported to stop cerebrospinal fluid (CSF) leakage and thus relieve pain. It is hypothesized that hemorrhage occurs due to a reduction in intracranial pressure following the loss of cerebrospinal fluid.[13] Displacement of the brain's tail may cause arachnoid membrane or venous structures to stretch, or both, eventually leading to bleeding. Although intracranial subdural hematoma is a seldom event, this fatal complication has been recorded after lumbar puncture.[25] Electron microscopic data on human bridge veins show that the thinnest part of their wall is in the subdural space and the thickest part is in the subarachnoid space.[3-7] Therefore, the veins in the subdural part are more fragile than the subarachnoid space.[26] The present study in rat pups showed that spinal anesthesia caused both subdural hematoma and epidural hematoma. Epidural and subdural hematoma occurred following lumbar puncture in cases of cerebral aneurysm, cerebral tumor, and cerebrovascular accidents. Tail movement of the brain may stretch spider web and venous structures, eventually leading to bleeding.[27-29] Thorsen has examined potential hemorrhages after spinal anesthesia.[28] In another study, two cases of subdural hematoma were reported that required surgical evacuation.[30] Another researcher reported a case of intracerebral hemorrhage after a lumbar puncture. His patient recovered with conservative treatment.[31] The veins of the cortical bridge in the subdural space have a thin wall and rupture due to shear force, so blood collects in the subdural space.[10] Subdural hematoma and epidural hematoma usually occur after a head injury, and because cerebral atrophy reduces tissue volume and causes more movement of the brain inside the skull, this condition is more common in older people.[31] Borger et al. in a study in North Wales (UK) reported a rate slightly higher than 8.2 per 100,000 populations for people over 65 years old.[32] Also, other researchers reported the incidence of chronic subdural hematoma in the age group between 70 and 79 years was 7.35 per 100,000 people per year.[11] Signs and symptoms of this complication include decreased concentration, pain, memory impairment, and confusion.[33,34] Behavioral changes, such as lethargy, emotional turmoil, poor personal health, and depression may be seen. Because of these symptoms, it is an error to identify them as people with dementia or other mental illnesses. Chronic alcoholism is also a risk factor and may lead to blood clots or head injury due to cirrhosis. If there are focal or side effects, they may present as speech disorders (dysarthria) or language problems and motor impairment.[35] Non-traumatic risk factors for chronic subdural hematoma or even epidural hematoma include coagulation disorders in patients on anticoagulant therapy or in people with liver failure, sepsis, or people on renal dialysis.[11] Occasionally, people caring for an elderly patient may experience changes in their behavior or symptoms of pain, confusion, and memory impairment. A high susceptibility index is required when older patients are anesthetized. The physical examination must be completed after the neurological evaluation to determine the focal or lateral symptoms or movement defects of these patients.[35] Leakage of CSF following Dural foramen and subsequent displacement of the brain tail, along with stretching on the vessels

sensitive to pain inside the skull and tantrum pain after the foramen must be taken into consideration. The pain is usually bilateral, and occipital, and it can affect the neck and shoulders.

This pain can be aggravated by standing, coughing, and pushing and it may be accompanied by nausea, vomiting, loss of appetite, changes in hearing acuity, tinnitus, and depression. The patient may also have diplopia and cranial nerve palsy. The safety of nerve units has been well established during a series of trials, even with anticoagulant and antiplatelet therapy.[36] Although the occurrence of intrathecal hematoma is rare, it can be a constant complication of lumbar puncture because it can cause permanent nerve damage and can be a concern for anesthesiologists.[2,6] Because the location of bleeding is concerned, there are still doubts about the location of the bleeding and where it was collected. Hemorrhages may occur in the extradural, subdural, or subarachnoid sections, and between different places, it mostly happens in the epidural space.[37] Spinal subarachnoid hematoma is very rare, but 54% of cases of acute spinal subdural bleeding are associated with bleeding disorders, 19% of which have defects in the hemostatic mechanism, and 35% of them with acute or chronic anticoagulant therapy. In addition to these coagulation changes, lumbar puncture (LP) was present in 33% of cases as an unpleasant cause. The acute spinal subdural hematoma was completely iatrogenic in 14% of cases, although in 7% of cases conditions such as pregnancy, dialysis treatment, diabetes mellitus, and arterial hypertension were present alone or in combination.[2]

In conclusion some problems during Dural perforation or return of cerebrospinal fluid. There are very few reports of acute localization of spinal subdural hematoma. This complication has been described as extra-arachnoid, being located "between two layers of the dura mater" that represents a "potential intradural space" as the location of subsequent bleeding and hematoma Preoperative neuroradiologic imaging confirms the extra-arachnoid aspect of acute subdural spinal hematoma and shows that it often presents as extradural bleeding as it was in our work. It usually starts with severe back pain that turns into loose paralysis, but the absence of low back pain does not rule out the presence of an intrathecal hematoma, as it was evidenced in the present rodent analyses.

List of acronyms

APTT - active partial thromboplastin time
CSF - cerebrospinal fluid
EDH - epidural hematoma
LMWH - low molecular weight heparin
LP - lumbar puncture
MRI - magnetic resonance imaging
PDPH - postoperative Dural headache
PTPJ - posterior temporal-parietal junction
SDH - Subdural hematoma

Contributions of Authors

All authors contributed substantially to the design and implementation of the study. All of the have read and approved the final edited typescript.

Acknowledgments

None.

Funding

The authors received no specific funding for this work.

Conflict of Interest

The authors declare no financial, personal, or other conflicts of interest.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Disclaimer

Submission: August 5, 2022
Revision received: August 26, 2022
Accepted for publication: August 26, 2022