Case Report
Treatment of organized chronic subdural hematoma using urokinase

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Received May 23, 2017; Accepted July 25, 2017; Epub October 15, 2017; Published October 30, 2017

Abstract: Craniotomy and membranectomy are widely accepted for the treatment of organized chronic subdural hematoma (CSDH); however, to our knowledge, the efficacy of burr hole irrigation and drainage with urokinase (UK) for organized CSDH has not been previously investigated. This case report describes 4 cases of organized CSDH, which were cured by UK injection into the hematoma cavity after one burr hole surgery. All patients were male (aged 55, 55, 58, and 76 years). One patient underwent an initial single burr hole craniotomy with a partial membranectomy and a burr hole 13 and 21 days after the first procedure. UK was subsequently injected into the hematoma cavity. One patient underwent burr hole surgery twice in 10 days, and UK was injected into the hematoma cavity after the second burr hole operation. Two patients underwent one burr hole operation and UK injection into the hematoma cavity following surgery. Organized hematoma drainage was satisfactory following UK administration. All patients exhibited full recovery without recurrence of the CSDH. There was no morbidity or mortality associated with UK injection. After a follow-up period of two months, a computed tomography (CT) scan indicated complete resolution of the hematoma in all 4 cases. These findings provide preliminary evidence that UK treatment after CSDH is a beneficial, safe, and effective treatment.

Keywords: Organized chronic subdural hematoma, urokinase, treatment

Introduction
Chronic subdural hematoma (CSDH) is one of the most common clinical entities of intracranial hemorrhage in neurosurgical departments [1]. Most CSDH cases are treated via one burr hole craniotomy with or without saline irrigation using closed-system drainage [2, 3]. Importantly, the failure of CSDH treatment via burr hole evacuation occurs because of organized CSDH [4-7]. To date, a large craniotomy with membranectomy is recommended as the sole approach for organized CSDH [4, 6, 7]. The clinical application of burr hole drainage combined with urokinase (UK) for intracranial hemorrhage has been widely reported and accepted; however, the efficacy of this approach for organized CSDH remains uncertain. Here, we report a novel technique that included UK injection into the hematoma cavity to drain organized CSDHs. The primary aim of this study was to evaluate the outcome and safety of UK injection in the subdural space for the treatment of organized CSDH. The findings indicated this approach led to optimal results in all four cases of organized CSDH.

Case report
Case 1

A 55-year-old man was admitted to our department following two months of headaches and one day of abnormal consciousness and vomiting. He had experienced a head injury two months prior, and a post-traumatic computed tomography (CT) scan indicated that there were no abnormal findings. He was diagnosed with CSDH in the left hemisphere via a CT scan on the day of admission (Figure 1A). Gait disturbance, urinary incontinence, and altered mental status were noted during the neurological examination after admission to our hospital. The routine laboratory results were unremarkable. An operation that included a one burr hole craniotomy and closed-system drainage was performed, and an organized hematoma was identified during the operation. The localized,
organized hematoma under the burr hole was absorbed during the surgery, and the patient’s headaches, consciousness, and gait disturbance remarkably improved one day after the operation with an alleviated mass effect (Figure 1B). Thirteen days after surgery, the patient exhibited dysphasia and seizures; a CT scan subsequently indicated an increased hematoma volume in the left hemisphere (Figure 1C). An operation that comprised a small craniotomy and partial membranectomy under general anesthesia was performed to evacuate most of the organized clot, and his symptoms disappeared the following day. Eight days after the second surgery, the patient complained of dysphasia and headache. An increased subdural hematoma volume with a low density was identified via CT scan (Figure 1D). Therefore, a second burr hole operation was performed, and the organized hematoma was identified during the operation. After the operation, 20,000 international units (IU) of UK (Tianjin Biochem Pharmaceutical Co., Ltd., Tianjin, China) was dissolved in three ml of saline and slowly injected into the clot. The tube was subsequently flushed with two ml of normal saline, closed for two hours, and then opened to drain. A 120 ml volume of liquefied blood was drained after three days of UK injection. On day four after the second burr hole, a CT scan indicated a small amount of residual hematoma (Figure 1E). The patient was discharged 16 days after the operation without neurological deficits. A two-month follow-up CT demonstrated a complete resolution of the hematoma (Figure 1F).

Case 2

A 76-year-old man presented with a 10-day history of dizziness and decreased muscle power
in the right side of his body, particularly the limbs. His previous medical history was unremarkable with the exception of diabetes. A physical examination indicated 80% strength in the right upper and lower extremities. A CT scan indicated a CSDH in the left hemisphere (Figure 2A). The routine laboratory results were unremarkable with the exception of the platelet number count, which was 63×10⁹/L. An operation that comprised a one burr hole craniotomy was performed when the platelet number count increased to 130×10⁹/L. The organized hematoma was identified during the operation. Approximately 10 ml of organized hematoma under the burr hole was absorbed, and the patient’s strength in the right limbs returned to 100% one day after the burr hole procedure. On day 10 after the surgery, the patient complained of a headache and motor disturbances of the right limbs (80% strength). A CT image indicated the subdural hematoma volume had increased with a mixed density in the left hemisphere (Figure 2B). A second burr hole was performed 11 days after the initial procedure, and the organized hematoma was identified. A CT scan on day 1 after the second burr hole indicates a substantial amount of residual CSDH (Figure 2C). A dose of 20,000 IU per day of UK was subsequently injected into the hematoma for three days. The total drainage volume was 130 ml in three days, and a CT scan demonstrated a very small amount of residual hematoma (Figure 2D). The patient exhibited a good post-operative recovery and had no neurological deficits when discharged. A two-month follow-up CT scan indicated excellent brain re-expansion (Figure 2E).

Case 3

A 58-year-old male was diagnosed with CSDH and underwent a burr hole craniotomy with closed-system drainage one month prior to admission to our hospital. The patient complained of a headache three days prior and was admitted to our hospital because of recurrent CSDH. His previous medical history indicated thrombocytopenia. CT and magnetic resonance (MR) images indicated left CSDH with multiple compartments and septations (Figure 3A-C). The routine laboratory results indicated that the platelet number count was 50×10⁹/L,
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and the fibrinogen was 135 mg/dL. An operation that comprised a one burr hole craniotomy was performed when the platelet number count and FIB were corrected. It was determined that the hematoma was partially organized during the operation. On day one after the surgery, approximately 10 ml of blood were drained. A UK dose of 20,000 IU per day was subsequently injected for three days. The total drainage volume was 70 ml. On day four after the second surgery, a CT scan indicated a small amount of residual hematoma (Figure 3D). The coagulation laboratory tests remained normal after the UK injection. Both the surgery and postoperative course were uncomplicated, and the patient was healthy with no recurrence two months after surgery. A two-month follow-up CT scan indicated complete brain re-expansion (Figure 3E).

Case 4

A 55-year-old male presented with a headache for one week. He had no history of head trauma. A MR image indicated left-sided CSDH with a heterogeneous signal intensity (Figure 4A and 4B). The routine laboratory results were unremarkable. The neurologic examination was normal after admission to our hospital. An operation that comprised a one burr hole craniotomy was performed, and the hematoma was determined to be organized, based on the intraoperative findings. A UK dose of 20,000 IU per day was subsequently injected through a drainage tube for three days. The total drainage volume was 140 ml, and a CT scan demonstrated a very small amount of residual hematoma on day three after the surgery (Figure 4C). The patient was discharged on the ninth day and continued to do well two months after surgery without recurrence. A two-month follow-up CT scan indicated total resolution of the hematoma (Figure 4D).

Discussion

CSDH represents one of the most frequent intracranial hemorrhages encountered in neurosurgical departments. In general, it is well accepted that burr hole craniotomy with closed-system drainage can achieve a good surgical prognosis as a treatment for CSDH. Or-
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Figure 4. CT scan of Case 4. A and B. Preoperative T1- and T2-weighted MRI images indicate a left-sided CSDH with a heterogeneous signal intensity. C. CT scan after three days of UK injections indicates a small amount of residual hematoma. D. Two-month follow-up CT scan indicates complete brain re-expansion.

Organized CSDH is a rare affliction with an incidence of 0.5-5.8% [4-7]. To date, a large craniotomy with membranectomy represents the only valid procedure for patients with organized CSDH. Here, we report a novel method of UK injection into the hematoma cavity in four cases of organized CSDH; the findings indicated favorable results.

Organized CSDH is characterized by thick membranes with multiple septations and formation of encapsulated areas of a solid consistency [8]. Subdural hematoma fluid does not typically clot on standing, and it also inhibits the normal clotting process [9]. However, in long-standing SDH, fibrous material gradually increases and reinforces the structure of multiple intrahematoma neomembranes, which form a completely solid structure [4]. To determine the optimal surgical strategy, it is useful to preoperatively determine the degree of hematoma organization. The characteristic findings of organized CSDH on CT or MRI have been fully discussed [4, 9-13]. If the initial CT indicates the hematoma may have a complex architecture, i.e., it is multi-lobulated and multi-layered with a prevalent solid component, a contrast enhanced MRI is indicated as the exam of choice [4, 10]. MRI can provide an accurate estimation of the age of the SDH, the intrahematomal structure of the CSDH, and the CSDH layering and membrane. As a result, MRI has been recommended as a basis for determining the operative procedure for CSDH [4, 8].

A small craniotomy with partial membranectomy procedure likely results in a limited surgical view. It is difficult to coagulate the fragile, new vessels, which may then contribute to re-bleeding [9]. Therefore, all reports recommend a large craniotomy with membranectomy as an effective approach for patients with organized CSDH [4, 6, 11]. Extensive removal of the organized hematoma and outer membrane and excision of the dura mater have also been proposed to achieve a successful outcome [12]. Ohkawa [13] has recommended stripping the dura mater from the skull and attaching it to the inner membrane with fibrine glue to completely obliterate the subdural space.

UK is also referred to as urokinase-type plasminogen activator (uPA) [14] and has been used as a fibrinolytic agent; its intrathecal administration has been demonstrated to be safe and efficacious in treatments regarding the subdural space, subarachnoid hemorrhage, intraparenchymal hematoma, and intraventricular hemorrhage [15-18]. Arginteanu previously used UK to enhance the drainage of hematomas and cured a recurrent acute subdural hematoma [18]. Neils reported that the administration of tissue plasminogen activator (tPA)
increased the drained hematoma volume and reduced the symptomatic recurrence rate of CSDH [19]. To date, the injection of UK into the hematoma cavity in organized CSDH treatment has not been reported. Our experience with these 4 patients provides robust, novel evidence that this approach is a safe procedure with no complications related to the administration of UK in such cases. In addition, UK administration via the subdural drain catheter led to the liquefaction of the organized hematoma and promoted drainage of the clot, which made a large craniotomy unnecessary. The addition of UK leads to a hyperfibrinolytic state, which subsequently results in no further hemorrhage, but a more liquefied hematoma; this favors the drainage of the organized hematoma after burr hole procedures. Compared with the UK treatment method, the performance of a large craniotomy for CSDH patients requires more time and is more invasive. Moreover, the aggressive removal of membranes may evoke postoperative seizures, which result from brain damage via traction in an attempt to remove the membranes with tight adherence to the cortex [4].

Although membranectomy has been considered a key technique that produces excellent results [4], in our four cases, we demonstrated that the brain completely re-expanded, where-as the hematoma membrane remained intact. These findings indicate full recovery of the organized CSDH does not require membranectomy. It is well known that the parietal membranes of hematoma vessels are fragile; thus, neomembranes undergo repetitive multifocal bleeding [4]. Therefore, these vessels are vulnerable to mechanical manipulation and carry a high risk of re-bleeding [1]. Moreover, UK administration in dissolving coronary artery clots has been associated with intracerebral hemorrhage in 1.6% of patients [20]. In our cases, no patient had a history of aspirin medication, and we adopted a reasonable dose of 20,000 IU (diluted in three ml of the saline solution), which has been demonstrated to be safe and effective in intraventricular hemorrhage [15, 17, 18]. After three UK injections, most organized hematomas were drained without re-bleeding, and the postoperative CT scans indicated brain re-expansion. The results of the 4 cases indicate this dose of UK is sufficient for the liquefaction of organized CSDH.

The toxicity of UK has not been previously discussed in the management of non-traumatic intraventricular hemorrhage [21]. In contrast, uPA favorably influences injured brain cells by delaying neurodegeneration; thus, it may be beneficial as a neuroprotection for brain injuries [22].

Despite these promising findings, several limitations regarding this study must be considered in the interpretation of these findings. First, it is a retrospective study and has limited cases from single institution. This limitation should be addressed in a larger, prospective study of organized CSDH treatment. Furthermore, UK has no effect on calcified or fibrotic tissue which can be found in rare cases of organized CSDH.

**Conclusion**

This case report described four cases with organized CSDH who obtained favorable results after UK injection into the hematoma cavity through a drainage tube. Based on the excellent recovery and reduced surgical invasion, this novel preliminary evidence supports the utility of this procedure for patients with organized CSDHs.

**Disclosure of conflict of interest**

None.

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