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Steroid for chronic subdural hematoma? A prospective phase IIB pilot randomized controlled trial on the use of dexamethasone with surgical drainage for the reduction of recurrence with reoperation

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Abstract

Background: Chronic subdural hematoma is a common neurosurgical condition especially in the aging population. Burr hole for drainage is an effective treatment, yet recurrence is reported at 8 to 22 % worldwide, and 1-year mortality rates could be as high as 32 %. Our previous study on the use of dexamethasone as a primary nonsurgical treatment showed good response in selected group of patients. This study aims to assess the efficacy of dexamethasone with surgical drainage in the reduction of recurrence requiring reoperation.

Methods: From October 2000 to September 2006, patients with chronic subdural hematoma admitted to the Prince of Wales Hospital, The Chinese University of Hong Kong, were randomized to surgical drainage with steroid versus surgical drainage only. The primary endpoint was symptomatic recurrence requiring reoperation.

Results: Two hundred forty-eight patients were recruited and consented for the randomization during the study period. One hundred twenty-two received both surgery and steroid (the intervention arm) while 126 received surgery only (the control arm). The recurrence rate requiring reoperation was 6.6 % (8/122) and 13.5 % (17/126), respectively ($p = 0.109$). There was no significant difference in complications such as chest infection ($p = 0.201$) or wound infection ($p = 0.987$). Favorable outcome (Glasgow Outcome Score 4–5) was 104/122 (85.2 %) in the intervention group versus 105/126 (83.3 %) in the control group, respectively ($p = 0.811$). Based on the recurrence rate in our study, we generate a potential sample size of at least 594 patients (type I error = 5 %, power = 80 %, two-sided test) to detect a significant difference.

Conclusions, brief summary, and potential implications: In this prospective pilot phase IIB randomized controlled study, steroid with surgical drainage had a lower recurrence with reoperation though statistically insignificant. It was safe with no significant difference in complication rates. This pilot study generates a potential sample size for a definitive larger double-blinded randomized controlled trial in the future.

Keywords: Chronic subdural hematoma; Steroid; Burr hole for drainage

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Background

Chronic subdural hematoma is a common neurosurgical condition especially in the aging population. Annual estimated incidence in the general population was 13.5 per 100,000 persons per year, and for those 65 years old or above, it was 58.1 per 100,000 persons per year [1]. The number of people older than 65 years is expected to double by 2050. Burr hole for drainage is an effective treatment, yet recurrence is reported at 8 to 22 % worldwide, and 1-year mortality rates could be as high as 32 % [2]. Our previous study on the use of dexamethasone as a primary nonsurgical treatment showed good response in selected group of patients [3]. This study aims to assess the efficacy of dexamethasone with surgical drainage in the reduction of recurrence requiring reoperation.

Methods

This is a prospective open labeled randomized controlled trial. From October 2000 to September 2006, patients with chronic subdural hematoma admitted to Prince of Wales Hospital, The Chinese University of Hong Kong, were recruited. Inclusion criteria include 18 years old or above and with informed consent. Exclusion criteria are those who are contraindicated to steroid. This included presence of sepsis or untreated infection, presence or history of peptic ulcer or gastrointestinal bleeding, development of uncontrolled hyperglycemia or poor diabetes control, development of delirium, history of Cushing's disease or history of osteonecrosis. Markwalder chronic subdural hematoma grading scale (MGS) was performed upon presentation. Grade 0 (neurologically normal) or grade IV (comatose with absent motor response to pain stimulus) patients were excluded. Patients or relatives who refused to consent were also excluded from the study. The randomization was performed by opening sealed envelops with the treatment arm designation. The control arm received burr holes for drainage only, and it was performed within 48 h after admission. The intervention arm received dexamethasone and surgical drainage. Dexamethasone was administered upon admission, with a treatment regime: dexamethasone 4 mg q6h for 4 days, then 2 mg tds for 3 days, then 1 mg bd for 3 days with famotidine. Burr hole for drainage would preferably be performed on day 2 after randomization, as long as the clinical condition stable. The primary outcome is recurrence with reoperation for drainage. It is open-label, and both surgeons and patients were not blinded to group assignment.

The assessment parameters included MGS upon presentation before the operation. Plain CT brain scan upon admission was performed, and maximum thickness of the chronic subdural hematoma was measured. During the hospital stay, there was daily clinical assessment of neurological status. CT brain scan was also performed on post-operative day 3, 2 months, 4 months, and 6 months. Re-drainage was defined as reoperation performed within 6 months after the first index operation when there were symptoms with confirmed radiological recurrence upon the progress CT scan. It was not considered as a recurrence or re-drainage as there were no symptoms radiologically on the same site. Any new hematoma which developed after 6 months were also considered as a new disease and was not considered as recurrence or re-drainage in this study. Complications were recorded including surgical site infection such as wound infection or empyema. Other general infections were documented including chest infection or urinary tract infection. Glasgow outcome scale (GOS) was performed at 6 months for all patients.

Results

Two hundred forty-eight patients were recruited and consented for the randomization during the study period. One hundred twenty-two were in the surgery and steroid group (intervention arm) while 126 were in the surgery only group (control arm). The background demographic of age and sex were comparable Table 1. The presenting MGS were comparable with no statistically significant difference. The recurrence rate requiring reoperation was 6.6 % (8/122) and 13.5 % (17/126), respectively ($p = 0.109$). The post-operative Glasgow Outcome Scale (GOS) were comparable in both groups, in which there was more good recovery (GOS 5) in the intervention group (81.1 %) versus the control group (72.2 %) though statistically not significant. There was more moderate disability (GOS 4) in the control group (11.1 %) versus the intervention group (4.10 %), yet it was not significant. There was no significant difference in complications such as wound infection ($p = 0.987$), subdural empyema ($p = 0.987$), chest infection ($p = 0.201$), or urinary tract infection (0.987). In the control group, there was a patient who died of intracranial hemorrhage and one of chest infection. In the intervention group, there was a patient who died of chest infection and subdural empyema. Overall, favorable outcome (Glasgow Outcome Score 4–5) was 85.2 % (104/122) in the intervention group versus 83.3 % (105/126) in the control group, respectively ($p = 0.811$). Based on the recurrence rate in our study, we generate a potential sample size of at least 594 patients (type I error = 5 %, power = 80 %, two-sided test).

Discussion

The use of steroid for chronic subdural hematoma dated back to 1968 [4]. At that time, it was used in conjuncture to bed rest and mannitol. In 1987, steroid was

Table 1 Background demographic, Pre-operative Markwalder Chronic Subdural Hematoma Grading Scale (MGS), Post-operative Glasgow Outcome Scale (GOS) and Post-operative complications

	Surgery only (control arm)	Surgery and steroid (intervention arm)	All	*p* value
Age	70.8	71.9	71.3	
Female	38/126 (30.2 %)	33/122 (27.0 %)	71	
Pre-operative plan CT brain scan findings				
Right	42/126 (33.3 %)	49/122 (40.2 %)	91	0.325
Left	52/126 (41.3 %)	58/122 (47.5 %)	110	0.387
Bilateral	32/126 (25.4 %)	15/122 (12.3 %)	47	0.013
Thickness	20.3 mm	22 mm	21.1 mm	
Pre-operative Markwalder Chronic Subdural Hematoma Grading Scale (MGS) upon presentation				
Grade I	89/126 (70.6 %)	99/122 (81.1 %)	188	0.074
Grade II	34/126 (26.9 %)	20/122 (16.4 %)	54	0.062
Grade III	3/126 (2.38 %)	3/122 (2.46 %)	6	0.709
Re-drainage rate	17/126 (13.5 %)	8/122 (6.56 %)	25	0.109
Post-operative Glasgow Outcome Scale (GOS)				
GOS 5 (good recovery)	91/126 (72.2 %)	99/122 (81.1 %)		0.131
GOS 4 (moderate disability)	14/126 (11.1 %)	5/122 (4.10 %)		0.066
GOS 3 (severe disability)	16/126 (12.7 %)	15/122 (12.3 %)		0.924
GOS 2 (vegetative state)	2/126 (1.59 %)	0/122 (0 %)		0.492
GOS 1 (death)	3/126 (2.38 %)	3/122 (2.46 %)		0.709
Post-operative complications				
Chest infection	1/126 (0.79 %)	5/122 (4.10 %)		0.201
Post-op fever	1/126 (0.79 %)	1/122 (0.82 %)		0.492
UTI	1/126 (0.79 %)	0/122 (0 %)		0.987
Wound infection	1/126 (0.79 %)	0/122 (0 %)		0.987
Subdural empyema	0/126 (0 %)	1/122 (0.82 %)		0.987

reported to be used as a primary nonsurgical treatment in 46 patients, in which 83 % were reported as "symptom-free" [5]. In our previous study conducted in 1998, we first clearly demonstrated the role of steroid as either a primary nonsurgical treatment or as an adjunct together with surgical drainage [3]. At the same time, the use of steroid with drainage versus steroid alone or drainage alone was compared in our paper, in which the use of steroid alone could have good outcome in selected group of patients. In another study in 2007, it even showed that the use of steroid in patients who have had operation for chronic subdural hematoma would have a smaller risk of death by threefold ($p = 0.006$) [6]. However, secondary intervention rate for use of surgery alone versus surgery and steroid can be up to 26.3 and 27.3 %, respectively, in another study [7]. So far, there is no agreed standardized treatment regime within neurosurgeons on this common neurosurgical condition [8].

Different methods have been proposed in the past to optimize the treatment outcome of this condition. For surgical technique, twist drill craniostomy, burr hole craniostomy, and craniotomy had been compared. It concluded that either twist drill or burr hole craniostomy should be considered as first tier treatment, in which our center adopted burr hole craniostomy [9]. Earlier studies did not show differences between craniostomy-irrigation versus craniostomy-closed system drainage [10, 11]. Site of drain placement was also explored such as subperiosteal drain versus subdural drain, which showed comparable outcome [12, 13]. Our recent comment on the latest meta-analysis of the use of subdural drain in chronic subdural hematoma expressed concern with the result predominant by one single randomized controlled trial findings [14, 15, 16]. At the same time, the role of steroid is continued to be explored.

A systemic review in 2012 on the use of steroid has concluded that the five observational studies provided class III evidence that suggests that the use of steroid in treating chronic subdural hematoma could be as safe as surgery [17]. However, the meta-analysis published in 2014 concluded that steroid offered no additional benefit to surgery [18]. There was no statistical difference in mortality or

recurrence rates but higher morbidity [18]. The majority of the morbidity was hyperglycemia up to 14.8 to 50 % [3, 7]. Infection was up to 9 % [7]. Only two patients were reported to have gastrointestinal bleeding [4, 7].

Our current study is the first pilot randomized study in the use of steroid with surgery versus surgery alone. MGS Grade 0 (neurologically normal) patients were excluded as they did not require immediate operative treatment by burr holes. Hence, it was not suitable for this group of patients to be randomized into either arm of the study as both proceed with burr hole for drainage, with or without steroid. MGS grade IV (comatose with absent motor response to pain stimulus) patients were also excluded as well. This is because this group of patients had profound neurological deficit and might not benefit from operation in the first place. At the same time, even if they had undergone burr holes, it was unlikely that steroid would have a significant impact on their neurological recovery. Furthermore, the aim of the study is to look into the recurrence, in which the recurrence rate in this group of patients might be counter-intuitively low because of the higher mortality [19].

The dexamethasone regime in this study was based on the regime in our previous study conducted from January 1998 to December 1999, which was published in British Journal of Neurosurgery in 2005. Dexamethasone was tapered in 2 weeks as adjunct to surgery or 3 weeks as monotherapy [3]. Dexamethasone has the longest biological half-life of all glucocorticoids (36 to 54 h). Its potency is seven times higher than prednisolone [20]. Various studies had demonstrated different steroid-tapering regime either as an adjunct therapy or as a monotherapy. In general, the duration of the regime is striking a balance between the efficacy versus the potential side effects. Surgery is still the mainstay of the treatment, and as an adjunct, the duration was usually shorter, whereas as a monotherapy, the duration is generally longer. One used a daily dose of 12 mg and tapered down 1 mg/day every 3 days [7]. One even used 16 mg tapering in 8 weeks as monotherapy [5]. In our study, we tapered down the dexamethasone in a shorter duration, from our previous regime of 14 days, to the current 10 days. It is interesting to see an even shorter regime in the latest ongoing randomized controlled trial to assess the efficacy of dexamethasone as an adjunct on reduction in the reoperation rate of chronic subdural hematoma (the DRESH study), in which it is a 6-day dexamethasone regime (16, 16, 12, 12, 8, and 4 mg/day) [20]. In our study, with a shorter steroid regime, the post-operative recurrence rate was clinically significant though statistically insignificant. At the same time, complication rates were comparable within the two groups. We are looking forward to the result of the ongoing double-blinded randomized controlled trial [20].

Other than dexamethasone, other nonsurgical treatment has been shown to be effective in a preliminary study as a medical monotherapy for chronic subdural hematoma. Hematoma was completely resolved in 17 of the 23 patients (77.3 %) 3 months after the treatment was initiated [21]. Whether atorvastatin is effective in reducing surgical recurrence remains to be tested in a future prospective study.

Conclusions

In this prospective pilot phase IIB randomized controlled study, steroid with surgical drainage has a lower recurrence with reoperation rate (6.6 and 13.5 %, respectively, $p = 0.109$). This pilot study generates a potential sample size for a larger definitive double-blinded randomized controlled trial in the future.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

WSP and TFS were the lead investigators and contributed with DYC to writing the report. WSP and TFS contributed in data collection. TFS and DYC contributed in data analysis. DYC contributed in drafting the manuscript. All authors read and approved the final manuscript.

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