Journal of Clinical Neuroscience 19 (2012) 961–964

Contents lists available at SciVerse ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical Study

A randomized, placebo-controlled pilot study of patients with spontaneous intraventricular haemorrhage treated with intraventricular thrombolysis

Nicolas K.K. King *, Jin Li Lai, Li Bing Tan, Kah Keow Lee, Boon Chuan Pang, Ivan Ng, Ernest Wang

Department of Neurosurgery, National Neuroscience Institute, 11 Jalan Tan Tock Seng, Singapore 308433, Singapore

ARTICLE INFO

Article history:
Received 26 August 2011
Accepted 28 September 2011

Keywords:
Blood clot
External ventricular drainage
Intraventricular hemorrhage
Urokinase
Thrombolysis

ABSTRACT

Intraventricular hemorrhage (IVH) occurring after spontaneous intracerebral hemorrhage (ICH) is an independent risk factor for mortality. The use of intraventricular urokinase (Uk) to reduce intraventricular blood clot volume and improve outcome was investigated. Patients with IVH requiring external ventricular drainage were recruited and randomized into a double-blind placebo controlled study. Assessments of collected cerebrospinal fluid (CSF) haemoglobin (Hb) and serial CT scans were performed. The study outcomes were: infection rates, length of stay in the intensive care unit, survival, National Institutes of Health Stroke Scale score; and modified Rankin Scale scores. Our results showed an increase in both the drained CSF Hb concentration in patients treated with Uk compared to placebo and in the rate of resolution clot volume. No differences were found in the other outcome measures but there was a trend towards lowered mortality in the group treated with Uk. Therefore, intraventricular Uk resulted in faster resolution of IVH with no adverse events.

1. Introduction

Intraventricular hemorrhage (IVH) occurs in up to 40% of patients with primary intracerebral haemorrhage (ICH).[1] Of an annual stroke incidence of 500,000 in the USA, the incidence of IVH is estimated to be 22,000 adults per year, with IVH-associated mortality of between 50% and 80%.[1,2] IVH associated with ICH is twice as common as that associated with spontaneous subarachnoid hemorrhage.[3]

IVH volume is also a significant risk factor for mortality independent of the ICH blood clot volume.[4,5] When ICH volume is >30 mL, there is a direct relationship with mortality; below this critical threshold, the mortality is lowered to about 20%.[4,6] Therefore, in those with a small ICH of <30 mL, the mortality may be related to the IVH.[1,3]

The current treatment strategy for IVH is centred on cerebrospinal fluid (CSF) drainage by external ventricular drainage (EVD), especially for acute obstructive hydrocephalus resulting from the intraventricular blood clot. However, the current approach has several limitations. Adams and Diringer[7] showed that hydrocephalus control through the use of EVD did not have any impact on survival, with only one patient out of 22 (4.5%) showing an improvement in both hydrocephalus and Glasgow Coma Scale score after EVD. Furthermore, experimental evidence suggests that the use of EVD alone does not accelerate the resolution of the IVH clot volume.[8] Thus, some authors have suggested that control of hydrocephalus on its own is insufficient to improve overall outcome.[9,10] This latter view is supported by animal experiments that show that reduction of both blood clot size and CSF blood burden were associated with improved outcomes.[11,12]

The use and safety of intraventricular lysis using either urokinase (Uk)[9,13–21] or tissue plasminogen activator (tPA)[22–28] in the treatment of IVH have been evaluated. Few controlled studies investigating intraventricular thrombolysis in IVH have been performed: in a randomised control trial, Naff et al.[9] demonstrated a significant increase in the rate of intraventricular blood clot resolution with the use of Uk compared to placebo; however, the study had to be terminated early due to the manufacturer's withdrawal of the Uk preparation.[9] Thus, we aimed to further investigate the use of intraventricular Uk in IVH in a prospective, randomised controlled double-blind study to assess the reproducibility of using Uk to reduce clot volume, and to assess its effect on clinical outcomes.

2. Methods

2.1. Participants

The study was approved by our institutional review board (SHS-IRB 2000/817/A) and informed consent was obtained from patients or their legally authorized representatives. Subjects were all admitted to the NeuroIntensive Care Unit (NICU) at the National Neuroscience Institute, Singapore, during the two-year period from 2006 to 2008. Data were prospectively collected.

* Corresponding author. Tel.: +65 63577191; fax: +65 63577137.
E-mail address: nicolas_kon@nni.com.sg (N.K.K. King).

0967-5868/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jocn.2011.09.030

Table 1
Baseline demographics and clinical outcomes of patients with spontaneous intraventricular haemorrhage treated with either urokinase or placebo

	Urokinase	Placebo	*p* level
Demographics			
No. patients	7	9	
Male:female ratio	0.75	3.5	0.15
Median age (years)	57.5	54.0	0.68
Admission median GCS	7	7	0.84
Admission median NIHSS	28	25	0.76
Mean IVH volume ± SD (mL)	56.9 ± 37.7	36.9 ± 31.0	0.22
Clinical outcomes			
Mean length of NICU stay (days)	10.1	7.3	0.22
VP shunting	1 (14%)	2 (22%)	0.69
No. patients with ventriculitis	1 (14%)	1 (11%)	0.85
Mortality (6-month)	1 (14%)	4 (44%)	0.31
Median NIHSS (30-day)	13.5	25	0.37
Median mRS (30-day)	5	5	0.68

GCS = Glasgow Coma Scale score, IVH volume = intraventricular haematoma volume on admission, mRS = Modified Rankin Scale, NICU = Neurointensive care unit, NIHSS = National Institutes of Health Stroke Scale, VP = ventriculoperitoneal.

Patients were recruited if they met the study inclusion criteria of: (i) a supratentorial intracerebral haematoma of <30 mL (as assessed on the presenting brain CT scan), with an associated IVH of any volume; and (ii) acute obstructive hydrocephalus requiring EVD. All patients had to have: (i) a diagnosis within 24 hours of the initial onset of symptoms; (ii) a known history of hypertension; and (iii) a pre-morbid modified Rankin Scale (mRS) score of 0 or 1. They also had to be between the ages of 16 years and 75 years. Those patients with infratentorial haemorrhage, clotting disorders, underlying intracerebral aneurysm, arteriovenous malformation or other vascular malformation, and traumatic IVH were excluded from the study.

In total, 16 participants were recruited (10 males; median age 56.5 years, range 46–69 years). The demographic data are shown in Table 1.

2.2. Randomisation and drug administration

Subjects were randomized using the random permuted blocks within strata method to receive either intrathecal Uk (25,000 IU Urokinase-Yoshitomi; Mitsubishi Pharmaceutical Corporation, Osaka, Japan) or saline (0.9%) of the same volume (7 mL) administered into the EVD. The differences in baseline characteristics are summarised in Table 1. There were no statistically significant baseline differences demonstrated between the two groups for age, sex, admission GCS, National Institutes of Health Stroke Scale (NIHSS) scores, and baseline volume of IVH.

The investigators and participants were blinded to the treatment received. Once diluted, the Uk solution was a clear, colourless liquid that could not be differentiated visually from the 0.9% saline solution used as placebo. The study drug or placebo was then administered via the EVD every 12 hours for three consecutive days under strict aseptic conditions. After administration of the intrathecal solution, the EVD port was closed for one hour, during which time the intracranial pressure (ICP) was continuously monitored via a pressure transducer. If there were a sustained ICP elevation of more than 20 mmHg during the one-hour period, the EVD port would be re-opened to restore drainage of CSF and to lower the ICP.

2.3. Outcome measurements

The concentration of haemoglobin (Hb, g/dL) was measured from the collected CSF drained from the EVD during the preceding 24 hours on consecutive days 1 to 5 after the start of treatment.

Serial non-contrast enhanced CT scans (5-mm slice thickness) were performed at baseline, 24 hours, 72 hours and 120 hours (5 days) to assess IVH volume after administration of either Uk or placebo. Volume of residual IVH was calculated using three-dimensional (3D) volumetric analysis software on a GE Advantage workstation (GE Healthcare; Little Chalfont, UK).

Clinical outcomes included the length of stay in the NICU and the rates of ventriculoperitoneal (VP) shunt insertion and of ventriculitis. Trained clinicians blinded to the treatment received also performed the assessment of the National Institutes of Health Stroke Scale (NIHSS) score and the mRS. Survival at six months was also determined.

2.4. Statistical methods

Data were entered into the Statistical Package for the Social Sciences version 16 (SPSS, Chicago, IL, USA) for analysis. Categorical data were compared using the Pearson chi-squared test while non-parametric data were compared using the Mann–Whitney *U*-test. Survival analysis was performed using the Kaplan–Meier method and resulting curves were compared using the log-rank test. Comparisons against the baseline were made using the analysis of variance (ANOVA). A $p < 0.05$ was considered significant.

3. Results

3.1. Haemoglobin concentration of the cerebrospinal fluid

The difference in Hb concentration in the CSF of both groups obtained at different time points after initiation of treatment is shown in Fig. 1. This showed that there was a peak in CSF Hb on day 2 after treatment in patients treated with Uk but not in the placebo group. There was some variability in the CSF Hb concentration, which accounted for the wider error bar on day 2. The difference between the two groups was significant ($p = 0.010$, ANOVA) with an overall mean increase in the CSF Hb concentration of 0.57 g/dL (190%) for patients treated with Uk compared to the placebo group.

3.2. Resolution of intraventricular hematoma volume

The residual volume of the intraventricular clot measured using 3D volumetric analysis based on serial CT scans on days 1, 3, and 5

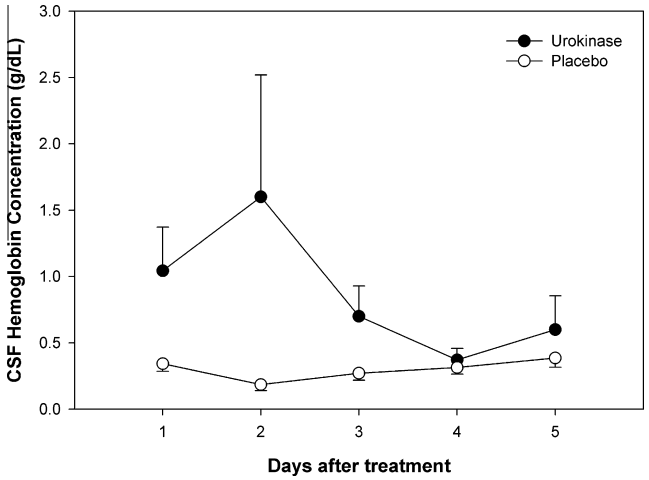

Fig. 1. A graph of mean haemoglobin (Hb) concentration in the cerebrospinal fluid (CSF) of patients with spontaneous intraventricular haemorrhage treated with urokinase (Uk, closed circle) or placebo (open circle) showing a significant difference between the two groups ($p = 0.010$, analysis of variance) with an overall mean increase in the CSF Hb concentration of 0.57 g/dL (190%) for patients treated with Uk compared to placebo. Error bars indicate standard error of the mean (SEM).