Corticosteroids in the Management of Hyponatremia, Hypovolemia, and Vasospasm in Subarachnoid Hemorrhage: A Meta-Analysis

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Key Words

Subarachnoid hemorrhage · Vasospasm · Steroids · Hyponatremia · Hypovolemia · Cerebral aneurysm

Abstract

Background: Cerebral vasospasm and sodium and fluid imbalances are common sequelae of aneurysmal subarachnoid hemorrhage (SAH) and cause of significant morbidity and mortality. Studies have shown the benefit of corticosteroids in the management of these sequelae. We have reviewed the literature and analyzed the available data for corticosteroid use after SAH. **Methods:** PubMed, EMBASE, and Cochrane electronic databases were searched without language restrictions, and 7 observational, controlled clinical studies of the effect of corticosteroids in the management of SAH patients were identified. Data on sodium and fluid balances, symptomatic vasospasm (SVS), and outcomes were pooled for meta-analyses using the Mantel-Haenszel random effects model. **Results:** Corticosteroids, specifically hydrocortisone and fludrocortisone, decreased natriuretic diuresis and incidence of hypovolemia. Corticosteroid administration is associated with lower incidence of SVS in the absence of nimodipine, but does not alter the neurological outcome. **Conclusions:** Supplementation of corticosteroids with mineralocorticoid activity, such as hydrocortisone or

fludrocortisone, helps in maintaining sodium and volume homeostasis in SAH patients. Larger trials are warranted to confirm the effects of corticosteroids on SVS and patient outcomes.

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Introduction

Cerebral vasospasm, hyponatremia, and volume contraction are common sequelae of aneurysmal subarachnoid hemorrhage (SAH) and are a cause of considerable morbidity and mortality [1, 2]. The search for pharmacological treatments of these sequelae has had minimal success with the exception for nimodipine, the only agent supported by widely accepted evidence for management of vasospasm.

Corticosteroids may be beneficial in managing these SAH sequelae, as they are anti-inflammatory agents that can also have mineralocorticoid effects with a potential to counteract hyponatremia and hypovolemia [3]. Therefore, we aim to assimilate published clinical data on sodium and fluid balance, vasospasm, and patient outcomes from studies utilizing corticosteroids to analyze their benefit in the management of SAH patients.

Methods

Search Strategy and Selection Criteria

The common evidence-based PICO framework was used to formulate the research question: do patients with aneurysmal SAH (population) treated with oral or intravenous corticosteroids (intervention) compared to those without treatment (control) have fewer sodium and fluid imbalances, lower incidences of symptomatic vasospasm (SVS), and better outcomes (outcomes)? Meta-analysis of Observational Studies in Epidemiology guidelines were used to perform this meta-analysis [4]. A systematic electronic search of titles and abstracts of published journal articles was done by A.M. Mistry using the following terms: ('subarachnoid hemorrhage' OR 'subarachnoid haemorrhage') AND ('steroid' OR 'steroids' OR 'corticosteroid' OR 'corticosteroids' OR 'mineralocorticoid' OR 'mineralocorticoids' OR 'glucocorticoid' OR 'glucocorticoids' OR 'hydrocortisone' OR 'fludrocortisone' OR 'dexamethasone' OR 'prednisolone' OR 'methylprednisolone') in PubMed (from 1966), EMBASE (from 1980), and Cochrane databases without language restriction in November 2015. Unpublished studies and conference abstracts were excluded. References obtained from these searches (236 from PubMed, 219 from EMBASE, and 69 from Cochrane) were imported into the reference manager EndNote X7 (Thompson Reuters, Philadelphia, Pa., USA), during which duplicate references were removed. Twenty-three candidate journal articles were identified by screening titles and abstracts for clinical studies of patients with aneurysmal SAH treated with and without corticosteroids. A search of their bibliographies led to the inclusion of one additional candidate study. After a full text review of these 24 articles, the following studies were excluded: 4 articles [5–8] with non-systemic corticosteroid administration; 4 [9–12] review articles; 1 article [13] involving corticosteroid administration after development of vasospasm; 2 articles [14, 15] where the control groups also received low amount of corticosteroids; 1 article [16] where not all patients in the control or treatment groups received corticosteroids; and those that were multi-drug [17], duplicate [18], side-effect only [19], and non-controlled [20]. Studies of tirilazad, a chemical compound structurally resembling a steroid but without glucocorticoid, mineralocorticoid, or other hormonal effects, were excluded; its effects have been summarized in a meta-analysis [21]. Seven final articles were included in the meta-analyses [22–28].

Data Extraction, Meta-Analyses, and Statistics

Cochrane Handbook for Systematic Reviews of Interventions [29] was referenced while performing the meta-analyses. For the 7 studies, the following variables were noted: study type; type of corticosteroid used and its dosing regimen; total number of patients, including high-grade SAH patients; and reported side effects in treatment and control groups (table 1). Authors of studies were contacted for clarifications to exclude duplicate data. Subsequently, the following data were extracted independently by 2 reviewers (A.M. Mistry and N. Ganesh Kumar): serum sodium (Na_{serum}), plasma osmolality, incidence of hyponatremia, sodium intake, natriuresis, fluid intake, urine output (UOP), incidence of hypovolemia, incidence of SVS, and patient outcomes. Mean values of Na_{serum} , sodium intake, natriuresis, fluid intake, and UOP together with Standard error (SE) were often graphically represented. Therefore, these figures were digitized using WebPlotDigitizer (version 3.8, May 2015; <http://arohatgi.info/WebPlotDigitizer>) to

obtain accurate values. Summary data were generated by weight-based average of means, and propagation of weight-based variances reported. These data were analyzed with unpaired 2-tailed t test. Statistical significance was set at $p < 0.05$.

Meta-analyses were conducted using the Review Manager (RevMan) software for Windows version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Dichotomous data were analyzed with Mantel-Haenszel random effects model. Odds ratios (ORs) used for the meta-analyses were calculated based on intention-to-treat analysis of published clinical data. Heterogeneity was assessed using the Cochran Q (chi-square), I^2 , and Tau^2 statistics. A p value < 0.1 from the chi-square test, $I^2 > 75\%$, and $\text{Tau}^2 > 1$ indicated considerable heterogeneity [29]. Sensitivity analysis was performed by omitting one study at a time to assess for changes in the significance of the summary effect size and by performing subgroup analysis of studies using nimodipine. Potential publication bias was evaluated by generating a funnel plot, plotting the ORs against variance. An asymmetric plot suggested possible publication bias. Risk of bias (specifically, selection, performance, detection, and attrition) in the studies was assessed by A.M. Mistry and E.A. Mistry independently by referencing the Cochrane risk of bias assessment tool [29].

Results

Study Characteristics

Table 1 lists the 7 articles included in the meta-analyses with their study design and the dosing regimen of the corticosteroid used. Cumulatively the risk of bias in these studies was high, tabulated in figure 1. Patients in these studies were nonpregnant adults. The primary mode of aneurysm treatment was clip ligation. Two studies included patients treated with endovascular coiling. In Gomis et al. [23], nearly half, and in Katayama et al. [25], 5 out of 71 patients were treated with endovascular coiling. Common side effects of corticosteroids were (in quantitatively reported incidences compared to control) hypokalemia (22/85 vs. 7/65) and hyperglycemia (8/50 vs. 3/50). Serious but rare adverse effects included gastrointestinal bleeds (2/85 vs. 0/86), pulmonary embolus (1/21 vs. 0/21), and heart failure (1/35 vs. 0/36).

Sodium and Fluid Balance

Three studies (2 utilizing hydrocortisone [25, 27] and one utilizing fludrocortisone [26]) reported sodium and fluid balance data in the form of sodium intake (sum of orally and intravenously administered sodium to maintain eunatremia) and natriuresis, as well as fluid intake (sum of orally and intravenously administered fluids to maintain the central venous pressure (CVP) > 8 cm H_2O) and UOP. Hypertension was maintained in 2 studies [26, 27]. These studies also reported Na_{serum} levels. Weight-

Table 1. List of studies included in the meta-analyses

Study	Study design	Treated/ control number	Number of high grade SAH in treated/control groups (grade)	Corticosteroid	Dosing regimen	Side effects in treated/control groups
Wijdicks et al. [28], 1988	Retrospective cohort (case series)	21/21 [42]	2/- (GCS $\leq$ 7)	Fludrocortisone	0.2 mg IV b.i.d. from $\leq$ SAHD 2–12 or day of operation	P.Ed -/-, $\downarrow$ K ⁺ 4/- $\uparrow$ BP 8/-
Hasan et al. [24], 1989	RCT	46/45	8/10 (GCS <12)	Fludrocortisone	400 μ g/day in 2 doses IV or PO from $\leq$ SAHD 3–12	P.Ed 2/2, $\downarrow$ K ⁺ -/-
Mori et al. [26], 1999	RCT	15/15	6/6 (HK III–IV)	Fludrocortisone	0.3 mg/day in 3 PO or via NGT doses from $\leq$ SAHD 3–8	$\downarrow$ K ⁺ 11/4, P.Ed 0/0, $\uparrow$ Glu 0/0 GIB 0/0
Moro et al. [27], 2003	RCT	14/14	3/5 (HK III–IV)	Hydrocortisone	IV (mg) taper started $\leq$ SAHD 2: 300 q6h from SAHD 0–10, then taper to SAHD 14	$\downarrow$ K ⁺ 6/3, $\uparrow$ Glu 4/3, $\downarrow$ Prot 4/2, GIB 0/0
Katayama et al. [25], 2007	RCT	35/36	13/11 (HK III–IV)	Hydrocortisone	IV (mg) taper from $\leq$ SAHD 3: 300 q6h from SAHD 0–10, 300 b.i.d. from SAHD 11–12, and 300 qday from SAHD 13–14	($\downarrow$ K ⁺ 1/0, $\uparrow$ Glu, $\downarrow$ Prot) (p < 0.001) GIB 2/0, CHF 1/0
Chyatte et al. [22], 1987	Prospective cohort	21/21	10/10 (Botterell 3–4)	Methylprednisolone	IV (mg/kg) taper started $\leq$ SAHD 3: 30 q6h $\times$ 12, 15 q6h $\times$ 4, 7.5 q6h $\times$ 4, 3 q6h $\times$ 4, and 1.5 b.i.d. $\times$ 2. 30 before operation	PE 1/0, $\uparrow$ Glu 4/0, P.Ed 0/1 DVTphlebitis 1/0, GIB 0/0
Gomis et al. [23], 2010	Double-blinded RCT	49/46	17/21 (HH III–V)	Methylprednisolone	16 mg IV/kg/day $\times$ 3 from $\leq$ SAHD 2–5	($\uparrow$ Glu, $\uparrow$ BP, Infxn) not significant

RCT = Randomized controlled trial; HK = Hunt and Kosnik; HH = Hunt and Hess; P.Ed = pulmonary edema; $\downarrow$ K⁺ = hypokalemia; $\uparrow$ BP = increased blood pressure; $\uparrow$ Glu = hyperglycemia; GIB = gastrointestinal bleed; $\downarrow$ Prot = hypoproteinemia; PE = pulmonary embolus; CHF = congestive heart failure; DVTphlebitis = deep vein thrombophlebitis; Infxn = infection; NGT = nasogastric tube; - = exact data not reported.

based average and error of these values were calculated for SAH days (SAHD) 3, 7, and 14, spanning the critical period for vasospasm [2].

Natriuresis and UOP

Natriuresis and UOP increased significantly from SAHD 3–7 in control (p = 0.03, p = 0.001, respectively; n = 65) and corticosteroid groups (p = 0.009, p = 0.0001, respectively; n = 64), and continued to remain high at SAHD 14 (fig. 2a, 3a). With corticosteroid treatment, the amount of natriuresis and UOP was statistically lower at SAHD 3 and 7 and continued to remain lower at SAHD 14 with near significance (p = 0.06, p = 0.07, respectively) compared to control.

Sodium and Fluid Intake

The amount of sodium and fluid required to maintain homeostasis increased significantly from SAHD 3–7 in control (p = 0.01, p = 0.02, respectively; n = 65) and corticosteroid groups (p = 0.008, p = 0.0001; n = 64; fig. 2a, 3a). While the amount of sodium required remained high in the control group, it lowered significantly in the corticosteroid group by SAHD 14 compared to SAHD 7 (p = 0.001). The amount of fluid required reduced significantly from SAHD 7–14 in both groups (control p = 0.01; corticosteroid p = 0.0001). With corticosteroid treatment, the amount of sodium and fluid required were significantly lower at SAHD 7 and 14 compared to the control group.

Fig. 1. Assessment of risk of bias in the included studies. Risk of 5 types of biases (columns) was assessed in the 7 included studies (rows). A high risk of bias is indicated by a red circle with a minus sign and a low of risk of bias indicated by a green circle with a plus sign. Empty cell indicates an unclear risk of bias.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)
Chyatte, 1987 [22]	⊖	⊖	⊖	⊖	⊕
Gomis, 2010 [23]			⊕	⊕	⊕
Hasan, 1989 [24]	⊕	⊕	⊖	⊖	⊖
Katayama, 2007 [25]					⊕
Mori, 1999 [26]					⊕
Moro, 2003 [27]					⊕
Wijdicks, 1988 [28]	⊖	⊖	⊖	⊖	⊖

Fig. 2. Meta-analyses of corticosteroids' effect on sodium balance. **a, b** Weight-based means calculated from three studies [25–27] (total n: corticosteroid = 64; control = 65). **c** Forest plot of studies reporting hyponatremia with summary odds ratio of 0.09 ([0.02–0.58], $p = 0.01$; $\text{Chi}^2 = 0.36$, $p = 0.55$; Tau^2 and $I^2 = 0$). p value sig-

nificance is designated by $^{\S} < 0.05$, $^{\dagger} \leq 0.01$, $^{\ddagger} < 0.005$, and $^* \leq 0.0005$. Corticosteroid used are designated by H = hydrocortisone and F = fludrocortisone. Error bars represent weight-based standard error of mean.

Fig. 3. Meta-analyses of corticosteroids' effect on fluid balance. **a** Weight-based means calculated from 3 studies [25–27] (total n: corticosteroid = 64; control = 65). **b**, **c** Forest plots of studies reporting hypovolemic incidences with summary OR of 0.27 (95% CI 0.10–0.74), $p = 0.01$; $\text{Chi}^2 = 0.24$, $p = 0.63$; Tau^2 and $I^2 = 0$) in

b and 0.13 (95% CI 0.02–0.89), $p = 0.04$; $\text{Chi}^2 = 2.34$, $p = 0.13$; $\text{Tau}^2 = 1.09$ and $I^2 = 57\%$) in **c**. p value significance is designated by § $p < 0.05$, ‡ $p < 0.005$, and * $p \leq 0.0005$. Corticosteroid used are designated by H = hydrocortisone and F = fludrocortisone. Error bars represent weight-based SE of mean.

Na_{serum} and Plasma Osmolarity

The mean Na_{serum} in the control group dropped significantly <140 mmol/l from SAHD 3–7 and stayed low ($n = 65$). With corticosteroid treatment, Na_{serum} stayed >140 mmol/l ($n = 64$; fig. 2b). Accordingly, plasma osmolarity decreased to ≤ 280 mOsm/kg over time without recovery but was maintained ≥ 288 mOsm/kg with hydrocortisone therapy studies [25, 27]. Pooled data [26, 27] demonstrated lower incidences of hyponatremia (Na_{serum} <135 mmol/l) lasting ≥ 48 h with corticosteroid therapy (summary OR 0.09; fig. 2c).

Volume Status

Pooled data demonstrated lower incidences of a volume decrement of >10% [24, 28] (summary OR 0.27; fig. 3b) and CVP <8 cm H₂O for ≥ 48 h [25–27] (summary OR 0.13; fig. 3c) with corticosteroid therapy.

Symptomatic Vasospasm

Six studies reported the effect of corticosteroid therapy on the incidence of SVS or delayed cerebral ischemia. However, SVS was heterogeneously defined, either as a

neurological decline (focal or general) with radiographic vasospasm (angiography [23, 25] or transcranial ultrasound [23]) or without objective evidence of vasospasm [22, 24]. Two studies did not provide a clear definition [26, 27]. Interestingly, only in one study [23], nimodipine was administered to all patients, including controls. Thus, meta-analysis was conducted with and without this study.

A trend toward reduction in SVS (summary OR 0.63 (95% CI 0.38–1.04), $p = 0.07$; fig. 4a) was noted with corticosteroid treatment in pooled meta-analysis of all studies. Sensitivity analysis with exclusion of the study utilizing nimodipine demonstrated reduction in SVS with statistical significance (summary OR 0.50 (95% CI 0.27–0.93), $p = 0.03$). No significant heterogeneity was noted among these studies. A potential for publication bias in this meta-analysis is indicated through the funnel plot (fig. 4b).

Patient Outcomes

Neurological outcomes were reported in 5 studies using the 5-point Glasgow Outcome Scale (GOS) at 6 months [23, 26, 27], last follow-up [22], and presumably at 1 month [24]. One study [25] reported outcome at

Fig. 4. Meta-analysis evaluating corticosteroids' effect on SVS. **a** The studies with total number of SVS events in control and corticosteroid groups with respective ORs and 95% CI and the weight of each study in the overall summary OR. This is represented

graphically in the forest plot. Corticosteroids used are designated by H = hydrocortisone, F = fludrocortisone, and M = methylprednisolone. **b** Funnel plot of studies included in the meta-analysis plotting the OR vs. SE.

1 month using the modified Rankin Scale (mRS). We calculated the ORs of good outcomes, defined as a GOS of 1–2 or mRS of 0–2 indicating functional independence of patients.

Corticosteroid treatment did not affect neurological outcomes (fig. 5a). Sensitivity analysis did not alter this

conclusion. No significant heterogeneity was noted among these studies. Funnel plot did not depict a potential for publication bias (fig. 5b). The proportion of patients with high grade SAH, which is known to influence outcome [30], were not statically different between control and steroid groups in these studies (table 1).

Fig. 5. Meta-analysis evaluating corticosteroids' effect on patient outcomes. **a** The studies with total number of SVS events in control and corticosteroid groups with respective ORs and 95% CI and the weight of each study in the overall summary OR. This is repre-

sented graphically in the forest plot. Corticosteroids used are designated by H = hydrocortisone, F = fludrocortisone, and M = methylprednisolone. **b** Funnel plot of studies included in the meta-analysis plotting the OR vs. SE.

Discussion

Although neurological outcomes in SAH patients were unaffected by corticosteroids, our analyses do indicate a potential role in decreasing natriuretic diuresis, incidence of hypovolemia, and SVS, especially in SAH patients who are unable to receive nimodipine. These effects were confirmed by a prospective study [16] of early fludrocortisone administration in a similarly treated population of SAH patients.

Mineralocorticoid Effect of Corticosteroids

An important sequelae of SAH is natriuresis with concomitant diuresis that can result in hyponatremic hypovolemia, which increases the likelihood of cerebral ischemia from vasospasm [1, 31]. Therefore, recent guidelines suggest avoiding hypovolemia and maintaining euvolemia to reduce SVS with class I evidence [1, 32–34]. However,

in a patient with natriuretic diuresis, this can be challenging. Volume resuscitation can exacerbate the natriuresis-driven diuresis and possibly worsen hyponatremia. One study demonstrated that despite large fluid intake to maintain CVP >8 cm H₂O, water balance in SAH patients becomes negative [26]. On the other hand, salt supplementation will increase natriuresis and further drive the concomitant fluid loss. Corticosteroids have mineralocorticoid actions that prevent natriuresis to maintain Na_{serum}. Reduction in natriuresis by corticosteroids decreases diuresis, the amount of fluid and sodium supplementation needed to maintain homeostasis, incidences of hyponatremia and hypovolemia, and therefore, SVS.

Anti-Inflammatory Role of Corticosteroids

It is hypothesized that vasospasm is related to the inflammatory response after SAH [35, 36]. However, presently no definitive evidence exists that corticosteroid ad-

ministration decreases vasospasm by altering the inflammatory response. Four studies examined the effect of steroids that have negligible to no mineralocorticoid effect [3], 2 studies [22, 23] utilizing methylprednisolone and 2 studies [14, 15] utilizing dexamethasone, thus emphasizing anti-inflammatory properties with little effect on natriuresis. Although one study [23] noted significant reduction in SVS in only high-grade SAH, these studies by themselves and in pooled analysis did not demonstrate a significant reduction in SVS (summary OR 0.98 (95% CI 0.61–1.57), $p = 0.94$; $\text{Chi}^2 = 3.98$, $p = 0.26$; $\text{Tau}^2 = 0.06$; $I^2 = 25\%$; SVS events/total n: corticosteroid = 61/211, control = 137/392). However, in three of these studies [14, 15, 23], both control and treatment groups received nimodipine, and in 2 studies [14, 15], the control groups also received a ‘low’ amount of steroids. These may decrease the detectable effects of these steroids. These studies did not demonstrate a significant improvement in neurological outcome as well. Although better outcomes were demonstrated in patients that received a higher amount of dexamethasone in one study [15], the number of high-grade SAH patients was significantly lower in the ‘high’-steroid group (19/105 vs. 42/137, $p = 0.03$) and may confound the outcome result. Hence, due to divergent study designs and lack of well-adjusted control groups, a clear conclusion is not formed regarding the anti-inflammatory effects of corticosteroids in the management of SAH.

Corticosteroids’ Influence on SAH Outcomes

Our meta-analysis did not demonstrate different neurologic outcomes with or without corticosteroids in SAH patients despite reducing SVS. Whether prevention of vasospasm influences outcome is debatable [37, 38]. One hypothesis is that the neurological outcome from SAH is dependent on the resulting direct brain injury, which is independent of and unaltered by vasospasm rescue. A recent study demonstrated that loss of consciousness at the onset

of SAH is a critical indicator of brain injury and a predictor of functional outcome [39]. Based on this hypothesis, corticosteroids may not ameliorate the brain injury caused by SAH, similar to the substantial evidence demonstrating no benefit of corticosteroids in the management of traumatic brain injury [40] or intracerebral hemorrhage [41].

Summary and Limitations

This meta-analysis demonstrates a value of corticosteroids in the management of SAH. Its use is associated with prevention of hyponatremia and hypovolemia through their mineralocorticoid effect. While this does not translate into improved neurological outcomes, it may help reduce SVS in the absence of nimodipine. These conclusions are limited by the weak strength of the evidence presented herein. Our meta-analyses included small studies demonstrating publication bias in which a majority of patients were treated with clip ligation and were not administered nimodipine. Therefore, large prospective randomized controlled trials are needed to confirm these conclusions, especially in patients treated with endovascular coiling and nimodipine.

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