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*Mini-Review*

# A Mini-Review of Magnesium Sulfate's Anti-Inflammatory, Immune, and Neuroprotective Mechanisms in Subarachnoid Hemorrhage

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**Abstract:** Subarachnoid hemorrhage (SAH) is a severe neurological condition frequently associated with devastating complications. This mini-review explores the therapeutic potential of magnesium sulfate (MS) in this setting. We conducted an updated search across several academic databases, focusing on articles examining MS's anti-inflammatory, immune-modulating, and neuroprotective properties in this setting. The findings suggested that MS can inhibit specific inflammatory pathways, reduce pro-inflammatory markers, modulate immune responses by inhibiting microglial activation, and offer neuroprotection through mechanisms such as NMDA receptor antagonism. However, despite the promising aspects of MS for SAH complications management, available clinical studies yield inconsistent outcomes. Additional research is necessary for full clinical validation.

**Keywords:** Subarachnoid Hemorrhage; Magnesium Sulfate; Magnesium; Inflammation; Neuroprotection; Immune response.

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## 1. Introduction

Subarachnoid hemorrhage (SAH) is a devastating neurological condition [1] affecting 6 to 9 people/100,000 per year with mortality rates as high as 50% [2]. SAH is frequently related to complications such as vasospasm and delayed cerebral ischemia [1], which are associated with inflammation and exacerbated neuronal injury [2]. In recent years, magnesium sulfate (MS) has been investigated as a therapeutic option in this setting due to its multiple mechanisms of action, including its anti-inflammatory effects, immune response changes, and neuroprotective properties [3,4]. Thus, we aimed to review the main features of those mechanisms, considering their importance for clinical trials and daily practice.

## 2. Methodology

For this mini-review, we conducted an updated search in the following databases: PubMed (last searched August 20, 2023), SciELO (last searched August 05, 2023), Embase (last searched August 10, 2023), and Google Scholar (last searched August 21, 2023). We used the following terms: magnesium sulfate, subarachnoid hemorrhage, inflammation pathways, immune response, neuroprotection, and cellular modulation. The outcomes of interest were MS's anti-inflammatory, immune, and neuroprotective effects, emphasizing

its interactions with specific inflammation pathways and cellular modulation in the post-SAH setting. We considered only papers published in English and Portuguese.

## 3. Results

### 3.1 Anti-inflammatory Activity

One of the central findings supporting the anti-inflammatory role of MS in SAH-related complications such as vasospasm is its inhibition of the NF-κB pathway [5]. The NF-κB pathway is an essential regulator of inflammation and has been implicated in multiple aspects of SAH-induced brain injury [6], including endothelial dysfunction [7] and blood-brain barrier disruption [8]. In vitro studies have demonstrated that MS can interfere with the nuclear translocation of NF-κB p65 subunit, thereby limiting its transcriptional activity [9]. This mechanism seems to be critical in curbing the production of pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-$\alpha$) [10], which are known to be associated with poor prognosis in SAH patients [11,12]. For instance, a retrospective analysis published in 2022 suggested that serum IL-6 peak was independently associated with long-term mortality in a multivariate model evaluating aneurysmal SAH patients [12]. Also, recently, clinical studies have shown a significant reduction in the serum levels of cytokines following the administration of MS [13], indicating a systemic anti-inflammatory action that could be beneficial.

Furthermore, MS has also been found to inhibit other pro-inflammatory mediators through mechanisms such as reduction of the cyclooxygenase-2 (COX-2) [14] and inducible nitric oxide synthase (iNOS) levels [15,16], both of which are commonly elevated in SAH and contribute to neural injury [17,18]. Studies have additionally shown that MS can modulate the activation of MAPK pathways [19], another critical element in the inflammation cascade [20].

### 3.2 Impact on Immune Response

MS may impact immune response by inhibiting microglial activation [21]. In the SAH context, activated microglia are a source of multiple inflammatory cytokines, such as TNF-alpha and IL-1β [22], and chemokines like C-C motif ligand 2 (CCL2) [23], contributing significantly to exacerbating brain injury [24]. These effects are pivotal given that microglial activation often catalyzes the chain of inflammatory events that ultimately lead to tissue damage and functional deficits post-SAH [21].

MS also affects cellular adhesion molecules, critical components in the immune response cascade. Studies have shown that MS significantly reduces the expression of key adhesion molecules like intercellular adhesion molecule-1 (ICAM-1) [25] and vascular cell adhesion molecule-1 (VCAM-1) [26]. Elevated levels of these molecules are implicated in the recruitment of peripheral leukocytes to the brain injury site [25-27]. Additionally, recent findings have suggested that MS might influence other immune system elements [28]. For example, MS modulates the activation of T-cells [29] and alters the secretion profile of astrocytes [30,31], two additional facets of the immune landscape following SAH that contribute to either neuroprotection or injury exacerbation [32].

### 3.3 Neuroprotective Role

The main neuroprotective property of MS lies in its N-methyl-D-aspartate (NMDA) receptor antagonism [33]. Through this mechanism, MS may reduce the hazardous impacts of glutamate excitotoxicity, a leading contributor to neuronal death post-SAH [34,35]. In 2018, Koning et al. demonstrated that rodent models treated with MS significantly reduced hippocampal neuronal loss in areas particularly susceptible to glutamate-mediated damage [36]. Another noteworthy MS's neuroprotective role is to mitigate calcium dysregulation [33,37], as elevated intracellular calcium levels can activate

enzymatic pathways, contributing to cell death [38]. Recently, studies showed that MS administration can reduce calcium influx via voltage-gated calcium channels, thereby diminishing neuronal vulnerability to calcium-mediated toxicity [33,39].

Another effect of MS is reducing reactive oxygen species (ROS) [40] through the enhancement of enzyme activity, such as catalase and superoxide dismutase, thus combating oxidative stress [41]. Finally, MS may modulate neurotransmitter levels [21,42] and stabilize neuronal membranes [43], which can be especially important in preventing further neural damage post-SAH [44]. A summary of the mechanisms above-described data is shown in Table 1.

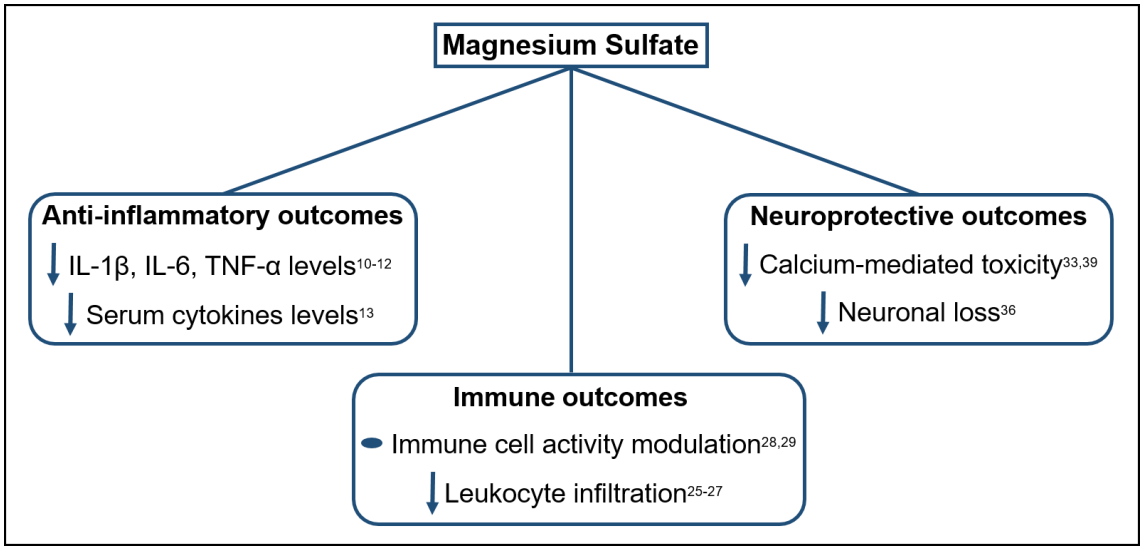
**Table 1:** Summary of MS's mechanisms of action with potential effect on SAH treatment.

| Effect | Mechanisms of Action |
|---|---|
| **Anti-inflammatory activity** | - NF-κB pathway inhibition [21]<br>- COX-2 [14] and iNOS modulation [15, 16]<br>- MAPK modulation [19] |
| **Impact on immune response** | - Microglial activation inhibition [21]<br>- ICAM-1 [25] / VCAM-1 [26] reduction<br>- T-cell activation modulation [28, 29]<br>- Altered astrocyte secretion [30, 31] |
| **Neuroprotective role** | - NMDA receptor antagonism [33]<br>- Calcium influx inhibition [33, 37]<br>- Antioxidative effects [40]<br>- Neurotransmitter modulation [21, 42]<br>- Neuronal membrane stabilization [43] |

**Legend.:** NF-κB – factor nuclear kappa B; COX-2 – cyclooxygenase-2; iNOS – inducible nitric oxide synthase; MAPK – mitogen-activated protein kinases; ICAM-1– intercellular adhesion molecule-1; VCAM-1 – vascular cell adhesion molecule-1; NMDA – N-methyl-D-aspartate.

The outcomes measures related to each cited MS's mechanism of action are exposed in figure 1.

**Figure 1:** Examples of MS's anti-inflammatory, immune, and neuroprotective outcomes.



## 4. Discussion

MS targets inflammation [5, 9], modulates the immune response [21, 23], and affords neuroprotection [33, 37], underscoring its versatility in addressing the multifaceted SAH complications [2]. MS's long-standing use in conditions like eclampsia [45] and severe asthma [46] supports its applicability in clinical practice. In eclampsia, MS has been successfully used to prevent and control seizures [45], while in severe asthma cases, it acts as a bronchodilator to relieve acute refractory exacerbations [46]. Although the pathophysiological underpinnings of eclampsia, asthma, and SAH are distinct, the proven safety profile and physiological impacts of MS in these conditions may offer additional assurance for its potential use in SAH treatment. However, several clinical trials published in recent years offered mixed results concerning the efficacy of MS in SAH [3, 47-49]. Some variables contributed to this uncertainty, including small sample sizes in some trials, unclear optimal dosage protocols, and methodological variances across different studies [3]. In summary, our quick review showed that translational knowledge and integrated clinical experience still need to be explored for assessing new strategies involving the MS's benefits for SAH complications management.

## 5. Conclusion

The MS's multimodal mechanisms of action may offer potential benefits in the context of SAH complications. However, the clinical application of MS remains an area of debate due to the varied outcomes from existing trials. While pre-clinical and some clinical evidence points toward the potential efficacy of MS, more extensive, well-designed, and standardized clinical studies are needed to solidify its role.

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