

Corticosteroid Treatment for Metastatic Spinal Cord Compression: A Review

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Abstract

Study Design: Narrative review.

Objective: Metastatic spinal cord compression (MSCC) is a very frequent complication among cancer patients. Presenting commonly as nocturnal back pain, MSCC typically progresses to lower extremity paresis, loss of ambulatory capabilities, and paraplegia. In addition to standard treatment modalities, corticosteroid administration has been utilized in preclinical and clinical settings as adjunctive therapy to reduce local spinal cord edema and improve clinical symptoms. This article serves as a review of existing literature regarding corticosteroid management of MSCC and seeks to provide potential avenues of research on the topic.

Methods: A literature search was performed using PubMed in order to consolidate existing information regarding dexamethasone treatment of MSCC. Of all search results, 7 articles are reviewed, establishing the current understanding of metastatic spine disease and dexamethasone treatment in both animal models and in clinical trials.

Results: Treatment with high-dose corticosteroids is associated with an increased rate of potentially serious systemic side effects. For this reason, definitive guidelines for the use of dexamethasone in the management of MSCC are unavailable.

Conclusions: It is still unclear what role dexamethasone plays in the treatment of MSCC. It is evident that new, more localizable therapies may provide more acceptable treatment strategies using corticosteroids. Looking forward, the potential for more targeted, localized application of the steroid through the use of nanotechnology would decrease the incidence of adverse effects while maintaining the drug's efficacy.

Keywords

spinal metastases, spinal cord compression, corticosteroid therapy, intrathecal drug delivery, steroid-conjugated nanoparticles

Introduction

Metastatic spinal cord compression (MSCC) is a common sequela arising from cancer, with an estimated yearly incidence of 2.2 cases per 100 000 people.¹ Among all cancer patients, spinal cord compression due to epidural tumor metastasis is estimated to develop in 5% to 14% of cases.² There are 3 mechanisms through which epidural MSCC might occur. First, bone metastases may expand into the epidural space, compressing the cord. Second, destruction of vertebral cortical bone can create instability and lead to vertebral body collapse, with displacement of bony fragments into the epidural space. Third, a paraspinal mass can cause neuroforaminal extension into the epidural space.² Clinical symptoms associated with spinal tumors are derived from the disruption of spinal cord tracts, nerve roots, and cerebrospinal fluid flow pathways with

specific symptoms dependent on the location of the tumor.³ The most common presenting symptom is nocturnal back pain, with other common symptoms including lower extremity weakness (with possible loss of ambulation), sensory loss, and altered bowel and bladder function. Patients may be either ambulatory or paraplegic at the time of diagnosis of MSCC.⁴

Standard treatment regimens for MSCC include radiotherapy with initial administration of corticosteroids, as well as

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decompressive surgery.⁵ Dexamethasone, commercially marketed as Decadron, is the corticosteroid of choice for the treatment of MSCC. However, a significant limitation of corticosteroid use is the high incidence of adverse systemic side effects associated with corticosteroid toxicity. The most frequent side effects include hyperglycemia, peripheral edema, infections, proximal myopathy, and gastritis.⁶ The incidence of these side effects increases in patients provided with higher doses of dexamethasone, suggesting a direct correlation between dose and the frequency and severity of symptoms.⁷ Consequently, the risks associated with dexamethasone treatment may outweigh the benefits, and the use of high-dose corticosteroids in treatment of MSCC has been called into question. However, treatment options that seek to maximize steroid efficacy while minimizing detrimental adverse effects are currently being researched and may prove beneficial.

Methods

A literature search was conducted to retrieve previous publications regarding the use of corticosteroids, specifically dexamethasone, in the treatment of MSCC. A PubMed search was performed using the terms “dexamethasone” and “spinal cord compression,” resulting in 108 search results. Publications that did not specifically address the use of corticosteroids and publications that did not include treatment of MSCC were excluded, resulting in the 7 articles reviewed here. The time period of included articles was 1977, at which time preclinical experiments in the use of dexamethasone to treat MSCC were beginning, to 2015.

Mechanism of Action

Overall, the main objective of steroid therapy is to decrease tissue edema and inflammation at the site of cord compression.⁵ In a study that examined the effects of dexamethasone on rat models of MSCC, Ushio et al⁸ found that the primary mechanism of action of the drug was to decrease the water content of the spinal cord overlying the tumor site. This reduction of spinal edema is the most probable action of the corticosteroid as it concurrently causes a rapid reduction in clinical symptoms associated with MSCC.⁸ In another rat study that examined more closely the effects of dexamethasone, a unidirectional blood-spinal cord transfer constant (K) was utilized in order to estimate the permeability-surface area product of the tissue capillaries. In rats with a compressed spinal cord, a dose-related reduction in K was observed 6 hours after the onset of dexamethasone treatment. Furthermore, a significant dose-related reduction of water content in the compressed cord was observed 42 hours following the onset of treatment. This finding suggested that dexamethasone acted in a dose-dependent manner on the reduction of capillary permeability to small molecules in the region of the compressed segment, decreasing water content and spinal cord edema at the site of compression.⁹ An alternative mechanism that has been proposed is steroid-induced hyperglycemia, thereby producing an osmotic

gradient across the blood-spinal cord barrier leading to a decreased water content of the spinal cord. The largest change in water content seemed to be based on the partial normalization of the blood-spinal cord barrier. However, in contrast to the study by Ushio et al,⁸ there was a more limited correlation between reduction in water content and improvement of clinical symptoms.⁹ Nonetheless, the apparent mechanism of action of dexamethasone seems to be decreased spinal cord edema due to a reduction in total water content of the surrounding tissue.

Preclinical Animal Studies

Animal models investigating the efficacy of dexamethasone treatment of MSCC provide differing conclusions. In a 1977 study by Ushio et al,⁸ rats received paraspinal inoculation of Walker 256 carcinoma cell suspension to induce spinal cord compression and were then divided into 3 groups receiving different dexamethasone regimens. The first group (Group I) received 10 mg/kg intramuscular dexamethasone twice daily for 3 days, beginning when the animals were graded as demonstrating “marked weakness” on a scale developed by Ushio. The second group (Group II) received 10 mg/kg intramuscular dexamethasone twice daily until death, again beginning when the animals were graded as demonstrating “marked weakness.” The third group (Group III) received 10 mg/kg intramuscular dexamethasone twice daily until death, beginning when the animals were graded as “paraplegia, no movement” on the Ushio scale. In Groups I and II, dexamethasone provided immediate improvement of weakness beginning on the second day of treatment (14 of 18 animals were able to walk or run). However, both groups began to deteriorate 4 days after the onset of treatment and eventually became paraplegic. In the third group, only 3 of the 9 animals showed transient improvement, suggesting that dexamethasone is only effective when administered prior to the onset of paraplegia. Based on this study alone, dexamethasone had no significant adverse effects on the survival time of the animals, indicating that dexamethasone could be a potentially useful treatment option in humans if given at high doses (10 mg/kg dexamethasone in rat models is approximately equivalent to 100-150 mg dexamethasone in a 70-kg man) prior to the loss of ambulatory capabilities.

Other animal studies offer less compelling evidence for the use of dexamethasone in high quantities. Using the same weakness scale developed by Ushio, Delattre and colleagues¹⁰ specifically examined the effects of dexamethasone dose on motor function and on associated adverse side effects. Spinal cord compression was induced in rats, which were then divided into 3 groups: a control group that received no treatment, a cohort that received 1.25 mg/kg dexamethasone intramuscularly twice daily (high-dose cohort), and a cohort that received 0.125 mg/kg dexamethasone intramuscularly twice daily (low-dose cohort). These doses correspond to an approximate dose in a 60-kg human of 150 mg/day and 15 mg/day, respectively. Treatment began after the rats reached Grade 5 weakness (“severe weakness, cannot stand, either paraplegic or severely

paretic”) on the scale developed by Ushio et al.⁸ These studies found that time to improvement was considerably reduced by administration of steroids. Additionally, the average weakness score was significantly lower in the subjects receiving dexamethasone treatment compared to the control rats. There was no significant difference in the degree of improvement between the high-dose and low-dose cohorts. However, the high-dose group did regain ambulatory capabilities at a mean of 3.6 days after the onset of treatment, compared to 5.1 days in the low-dose group. This indicates that higher doses of dexamethasone do shorten the time required until ambulation is possible, even if treatment was begun after the onset of paraplegia or severe paresis. The mortality rate in the high-dose group was much higher than in the low-dose and control groups, suggesting significant adverse effects of the steroids in high doses. All animals in the high-dose group died within 20 days, while all but 2 rats in the low-dose and control groups lived to at least 30 days. There was no comment as to whether or not the rats remained ambulatory until death, or if they deteriorated to paraplegia. On autopsy, it was found that 4 of the 5 animals treated with high-dose dexamethasone had evidence of severe infection, and one of the 5 animals showed gastrointestinal perforation with bleeding. These results demonstrate that, while the administration of dexamethasone in higher doses does reduce time to ambulation, the associated systemic side effects contradict a recommendation for high-dose steroid treatment.

In a separate rat study, Delattre et al⁹ induced MSCC and divided the rats into 4 groups once they reached Grade 4 on the Ushio scale (“marked weakness, able to stand but not to walk”): a control group, a low-dose group (receiving 0.1 mg/kg intravenous dexamethasone), an intermediate-group (receiving 1 mg/kg intravenous dexamethasone), and a high-dose group (receiving 10 mg/kg intravenous dexamethasone). These dose levels are approximately equivalent to 1.5 mg, 15 mg, and 150 mg, respectively, in a 70-kg adult human. Improvement or stabilization of clinical progression, reduction in water content of the compressed spinal cord 42 hours posttreatment, and reduction of the unidirectional transfer rate constant of AIB (aminoisobutyric acid, a function of blood-spinal cord barrier) 6 hours posttreatment were all examined. On all 3 measures, the animals that were administered higher doses of dexamethasone showed greater improvement than animals that were administered lower doses. Furthermore, improvement was directly correlated with level of dosage, with the high-dose group showing the most significant improvement 24 hours and 40 hours after treatment.

Based on these animal studies, the benefits of using higher doses of dexamethasone for the treatment of spinal cord compression are clear. Physiological indicators of tumor-associated edema reduction were more drastic in animals that received higher levels of steroid treatment, as were the animals’ abilities to maintain or regain motor function following treatment (Table 1).⁸⁻¹⁰ On the other hand, severe and potentially fatal side effects were found in rats treated with higher doses of dexamethasone. Moreover, the high-dose rats had considerably

lower survival rates than their low-dose counterparts.¹⁰ While high doses of dexamethasone reduce clinical symptoms and seem beneficial in animal studies, the associated, and frequently occurring, systemic side effects raise questions about the safety of such treatment.

Clinical Studies

When examining clinical studies, the potential dangers of high-dose dexamethasone treatment over prolonged periods become more obvious. A 1980 study conducted by Greenberg et al¹¹ treated patients with dexamethasone followed by radiotherapy. Patients received an initial intravenous bolus of 100 mg dexamethasone, followed by 3 days of 24 mg oral dexamethasone 4 times per day with tapering and cessation of dexamethasone on day 14 of treatment. Fifty-seven percent of all patients were ambulatory after steroid treatment, with 28% of those patients being nonambulatory before the onset of treatment. No patients that were completely paraplegic, however, regained ambulatory abilities following treatment. Despite these results, the experimenters concluded that steroid effects on motor function were difficult to assess since radiation therapy was begun immediately following dexamethasone treatment. Of note, a serious complication (a nonfatal ruptured duodenal ulcer on day 4 of treatment) concurrent with steroid treatment was found in only 1 of the 83 patients, though this was not definitively linked to dexamethasone treatment. Looking at this early study in isolation, the effect of high-dose steroids on pain relief is encouraging, but the effects on motor function proved inconclusive due to radiation therapy occurring immediately after steroid therapy. Furthermore, no examination of differences between high-dose and low-dose dexamethasone was conducted, requiring further research.

A 1989 study conducted by Vecht et al¹² yielded few differences between high-dose and low-dose dexamethasone cohorts. Intravenous administration of either 10 mg (low-dose) or 100 mg (high-dose) dexamethasone, both followed by 16 mg dexamethasone orally per day, in patients with MSCC provided a significant decrease in pain rating (from an average of 5.2 prior to treatment to an average of 1.4 one week posttreatment). However, the 2 different dose levels provided no significant difference in pain relief, ambulation, or survival. While this finding would lead one to believe that the administration of high-dose steroids poses no apparent danger to the patient, it is important to note that the high-dose cohort was only given a significantly higher amount of dexamethasone (100 mg as opposed to 10 mg) for 1 day. After this point, all patients were given 16 mg dexamethasone daily, which may substantially lessen the possibility of toxic side effects thought to be associated with high-dose steroid treatment.

Specific investigation of dexamethasone treatment on steroid-related toxicity was piloted in a 1987 retrospective study.⁶ In this study, the development of toxicity was found to directly correlate with increased doses of dexamethasone. Specifically, the incidence of toxicity was 75% in patients whose total cumulative dexamethasone dose was >400 mg,

Table 1. Dexamethasone Effects on MSCC, Dose-Dependent Outcomes, and Systemic Side Effects in Animal Studies

Study	Group I	Group II	Group III	Group IV	Effect of Dexamethasone on MSCC	Effect of Dexamethasone Dose	System Side Effects
Ushio et al ⁸	10 mg/kg IM dexamethasone 2×/day for 3 days, beginning at "marked weakness"	10 mg/kg IM dexamethasone 2×/day until death, beginning at "marked weakness"	10 mg/kg IM dexamethasone 2×/day until death, beginning at paraplegia		<ul style="list-style-type: none"> Transient improvement (deterioration 4 days after treatment onset) 		
Delattre et al ¹⁰	Control (no dexamethasone treatment)	1.25 mg/kg IM dexamethasone 2×/day, beginning at "severe weakness"	0.125 mg/kg IM dexamethasone 2×/day, beginning at "severe weakness"		<ul style="list-style-type: none"> Reduced time to improvement Improved score on Ushio weakness scale 	<ul style="list-style-type: none"> No difference in average weakness score Reduced time to improvement in high-dose cohort Increased mortality rate and decreased time until death in high-dose cohort 	<ul style="list-style-type: none"> Severe infection GI perforation with bleeding
Delattre et al ⁹	Control (no dexamethasone treatment)	0.1 mg/kg IV dexamethasone sodium phosphate 2×/day, beginning at "marked weakness"	1 mg/kg IV dexamethasone 2×/day, beginning at "marked weakness"	10 mg/kg IV dexamethasone 2×/day, beginning at "marked weakness"	<ul style="list-style-type: none"> Stabilization or slowing of clinical progression of motor deficits 	<ul style="list-style-type: none"> Dose-related improvement/stabilization of clinical progression of motor deficits Dose-related reduction in water content of compressed spinal cord Dose-related reduction of unidirectional transfer rate constant of AIB 	

Abbreviations: MSCC, metastatic spinal cord compression; IM, intramuscular; IV, intravenous; AIB, aminoisobutyric acid.

compared to a toxicity incidence of 13% in patients whose total cumulative dose was <400 mg. Furthermore, development of steroid-related toxicity directly correlated with duration of dexamethasone treatment, with a 76% incidence of toxicity in patients receiving steroid treatment for longer than 3 weeks, compared to a 5% incidence of toxicity in patients receiving treatment for less than 3 weeks. The most common toxicities found among the patients in this study were infection (28 separate infections in 13 patients), hyperglycemia, and proximal myopathy.

Similarly, in a 1992 prospective study by Heimdal et al⁷ that examined the dose level of dexamethasone on steroid toxicity, patients in a high-dose group were started on a 96 mg intravenous loading dose, which was then tapered to zero over a 15-day period. Patients in a normal-dose group were administered 4 mg intravenous dexamethasone 4 times per day initially, then tapered to zero over a 15-day period. The high-dose group resulted in side effects in 28.6% of patients, with 14.3% experiencing serious side effects. Meanwhile, 7.9% of the normal-dose group exhibited some side effects, with none of the patients experiencing serious side effects. Because the high-dose group resulted in a significantly higher rate of side effects but was not associated with a significant increase in ambulation rates after treatment (57.1% in the high-dose group vs 57.9% in the normal-dose group), the experimenters concluded that high doses of dexamethasone are not beneficial for the management of MSCC and result in unacceptable rates of adverse side effects.

In contrast to the study by Heimdal et al,⁷ which clearly demonstrated the potential for harmful side effects of high-dose steroids, other studies support the use of dexamethasone in high doses. In a 1994 study led by Sørensen and colleagues,¹³ patients were divided into a control group and a dexamethasone treatment group. The patients in the dexamethasone treatment cohort were initially given 96 mg intravenous dexamethasone, followed by 24 mg oral dexamethasone 4 times per day for 3 days, followed by tapering of treatment over a 10-day period. Patients in both groups were also treated with radiation therapy, which occurred on days 1 to 7 in the case of the dexamethasone treatment group. Preservation of gait in ambulatory patients, and restoration of gait within 3 months of treatment in nonambulatory patients, was seen in 81% of patients in the dexamethasone treatment group, compared to 63% of the patients who received no dexamethasone treatment. Significant side effects (hypomania, psychosis, and a perforated gastric ulcer) were reported in 3 patients belonging to the high-dose dexamethasone group. Despite the apparent clinical value of adjunct dexamethasone therapy, an optimal dosing regimen was not established because of the relatively high rates of serious side effects compared to radiation monotherapy. As a whole, such clinical studies provide differing accounts of the success of high-dose dexamethasone treatment (Table 2).^{5,6,12,13} Due to the direct correlation between dexamethasone dose escalation and increase in system side effects, the efficacy and safety of high-dose corticosteroid administration for treatment of MSCC remains uncertain.

Discussion

Further studies must be conducted to more precisely determine the optimal dexamethasone treatment regimen for both ambulatory and nonambulatory patients, taking into consideration both the benefits of low- versus high-dose dexamethasone as well as the associated risks of corticosteroid toxicity (Table 3).¹⁴ Though animal and human studies agree that steroid treatment is a viable option for MSCC, it is now widely accepted that high-dose regimens hold a higher risk of steroid-related adverse effects. Because of this discrepancy, there are conflicting reports as to whether or not the risks outweigh the benefits of high-dose dexamethasone regimens. In high amounts, corticosteroids may lead to a variety of systemic symptoms, limiting the recommendation of a well-defined high-dose dexamethasone treatment plan in MSCC patients.

Based on analysis of 3 controlled trials (one of which was double blinded,¹⁵ one of which had observers blinded,¹² and one of which had neither participants nor observers blinded⁴), there was no significant benefit to ambulation, 2-year survival, pain relief, or urinary continence as a result of treating with high-dose dexamethasone versus moderate-dose dexamethasone.¹⁵ There was, however, a significant increase in drug-related adverse effects (specifically perforated gastric ulcer, psychoses, and deaths from infections) in patients receiving high-dose treatment. Because of this, the value of high-dose dexamethasone regimens is yet again called into question. A recent suggested dose of dexamethasone for treatment of spinal cord compression is an initial 10 mg intravenous loading dose, followed by 6 to 10 mg every 6 hours.³ Compared to an older alternative that proposes a 96 to 100 mg intravenous loading dose followed by 24 mg every 6 hours, this more current recommendation is much more cautious. However, these plans are merely suggestions, and the optimal dexamethasone dose is still not yet definitively established for the treatment of MSCC.

While the use of corticosteroids such as dexamethasone very clearly correlates with an increase in adverse effects due to drug toxicity, developing new treatments involving the use of localizable drug delivery may prove beneficial. The intrathecal delivery of drugs has been used previously for anesthesia and cancer pain management in order to minimize the potential for adverse systemic side effects associated with the drug. Intrathecal delivery, along with incorporation of steroid-conjugated nanoparticles, allows for targeting and maintenance of the drug within a desired area of the spinal cord. While nothing has been demonstrated previously using localized delivery in the spinal cord, studies have demonstrated effective treatment of malignant glioma using nano-enabled steroids to enhance localized drug delivery past the blood-brain barrier.¹⁶ In vitro studies utilizing magnetic drug targeting have been performed in which magnetic nanoparticles are injected and an external magnetic field is applied, thereby localizing the nanoparticles and the effects of the conjugated drugs.^{17,18} In this human spine model, external magnets with surface strengths of 0.396, 0.507, and 0.528 Tesla were successful in attracting the nanoparticles and confining the majority to the target region after a

Table 2. Dexamethasone Effects on MSCC, Dose-Dependent Outcomes, and Systemic Side Effects in Clinical Studies

Study	Group I	Group II	Effect of Dexamethasone on MSCC	Effect of Dexamethasone Dose	Systemic Side Effects
Greenberg et al ¹¹	100 mg initial IV dexamethasone, followed by 3 days of 24 mg orally 4×/day, then tapered to zero at day 14		<ul style="list-style-type: none"> 57% of patients ambulatory following treatment, 28% of whom were nonambulatory before treatment onset No regain of ambulatory abilities in patients who were completely paraplegic pretreatment onset Significant pain relief Significant decrease in pain rating 		<ul style="list-style-type: none"> Nonfatal ruptured duodenal ulcer on day 4 of treatment in one patient
Vecht et al ¹²	10 mg initial IV dexamethasone, followed by 16 mg daily orally	100 mg initial IV dexamethasone, followed by 16 mg daily orally		<ul style="list-style-type: none"> No significant difference in pain relief, ambulatory capacities, or survival No significant difference in rate of ambulation posttreatment 	
Heimdal et al ⁷	4 mg initial IV dexamethasone 4×/day, then tapered to zero at day 15	96 mg initial IV dexamethasone, then tapered to zero and day 15		<ul style="list-style-type: none"> 28.6% incidence of side effects in high-dose group (GI bleeding, GI perforation, pneumonia, hyperglycemia, and wound infection), compared to 7.9% incidence of side effects in normal-dose group (pneumonia and wound infection) 14.3% incidence of serious side effects in high-dose group, compared to 0% incidence of serious side effects in normal-dose group 	
Sørensen et al ¹³	Control (no dexamethasone treatment)	96 mg initial IV dexamethasone, followed by 3 days of 24 mg orally 4×/day, then tapered to zero at day 14	<ul style="list-style-type: none"> Preservation of gait in ambulatory patients Restoration of gait in non-ambulatory patients 	<ul style="list-style-type: none"> Success of treatment in 81% of dexamethasone cohort, compared to 63% in control cohort 	

Abbreviations: MSCC, metastatic spinal cord compression; IM, intramuscular; IV, intravenous.

Table 3. Benefits and Contraindications of Using High-Dose Dexamethasone in MSCC Treatment.

Benefits	Contraindications
<ul style="list-style-type: none"> • May be used in conjunction with radiation therapy • Preservation of gait in ambulatory patients • Restoration of gait in nonambulatory patients • Relief of pain • Slowing of progression of clinical symptoms 	<ul style="list-style-type: none"> • Cannot be localized to site of cord compression • High incidence of adverse systemic side effects • Presence of serious (fatal) systemic side effects

Abbreviation: MSCC, metastatic spinal cord compression.

15-minute duration, regardless of the distance between the injection site and the target site. Such magnetic drug targeting methods will next be applied in animal models and in clinical trials in order to determine the viability of such technology in vivo. If successful, the administration of corticosteroids, such as dexamethasone, can be used as an effective treatment method for MSCC, all while limiting any adverse steroid-related side effects as much as possible.

Conclusions

Metastatic spinal cord compression is a frequent problem among cancer patients, leading to back pain, lower extremity weakness, and potential loss of ambulatory capabilities. Treatment plans include radiation therapy, surgery, and steroid (dexamethasone) treatment, though defined guidelines for corticosteroid treatment have yet to be produced. Animal studies of corticosteroid treatment provided initial backing of the benefits of using dexamethasone, demonstrating significant improvements in clinical symptoms as a result of high-dose steroid treatment. Findings from human clinical studies of steroid treatment of MSCC tend to offer less support of the administration of dexamethasone in high doses over low or moderate doses, and highlight the high frequency of adverse side effects linked to high-dose steroid treatment. Although the risks accompanying high-dose dexamethasone are indisputable, the development of localizing magnetic nanoparticles could offer more efficacious treatment plans that would eliminate the adverse side effects. Upcoming research is being pursued in order to determine the optimal dose of dexamethasone in treating MSCC and to assess the prospect of incorporating drug-targeting technology into the current treatment plan.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Mehta receives funding from an AO Foundation Young Investigator Award. Dr Linninger has a patent for nanoparticle drug delivery pending. The remaining authors report no disclosures.

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