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Research Article

Anti-inflammatory effects of boron alone or as adjuvant with dexamethasone in animal models of chronic and granulomatous inflammation

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ABSTRACT

Background: Side effects of anti-inflammatory agents are a major problem during clinical use. The development of a newer, effective, and safe anti-inflammatory agent should be considered. Boron-containing compounds are found effective as anti-inflammatory agents with relatively low side effects. We aimed to evaluate the anti-inflammatory activity of boron in animal models of chronic and granulomatous inflammation.

Methods: Sixty-six Wistar rats were allocated into five groups; 1st (6 rats) treated with vehicle only without induction as a negative control; 2nd (12 rats) allocated into two subgroups, treated with vehicle only, with induction of chronic and granulomatous inflammation, as appositive control. 3rd group (24 rats) allocated into four subgroups, treated with different doses of boron (3 and 6 mg/kg) in both models. Fourth group (12 rats) treated with dexamethasone (1 mg/kg) in the same models. 5th group (12 rats used) treated with boron (3 mg/kg) with dexamethasone (1 mg/kg) in the same models.

Results: Boron, in a dose-dependent pattern significantly decreases inflammation in rat models of chronic and granulomatous inflammation. Combination of boron with dexamethasone significantly suppresses inflammation in both models, which is significantly higher than all of the effects produced by other approaches of treatment.

Conclusion: Boron, in a dose-dependent pattern, effectively suppresses formaldehyde-induced chronic inflammation and cotton pellet-induced granuloma in rats when used alone or as an adjuvant with dexamethasone. It may be considered as a potential treatment for chronic inflammatory conditions.

Keywords: Boron, Chronic inflammation, Granuloma, Rats

INTRODUCTION

Boron is well-known as an essential trace element for plants, but has only recently been recognized to be a possibly important physiological role in humans. Adequate evidences indicate that subjects consume less boron than required demonstrate health related problems in the bone and brain, and inflammatory reactions suggesting a highly expected role in maintaining normal health.[1,2] There are only limited number of data that correlate boron intake or plasma levels with human pathologies other than certain kinds of tumors. However, decreased hair contents of boron,[3] and low environmental boron[4] have been associated with Kashin–Beck disease in China, and low plasma boron level has been associated with rheumatoid arthritis.[5] Many experimental animal and human studies provided evidence for the effective and safe use of boron for treating certain types of osteoarthritis.[6] Regarding the relationship between boron intake and the prevalence inflammatory joint diseases, many researchers have discovered that abundant intake

of dietary boron can confer strong protection against the development of these diseases.[7,8] According to the outcome of many experimental studies, the suggested hypothesis for this effect of boron includes reduction in the risk of inflammatory disease by downregulating enzymes of the inflammatory response, in addition to well-recognized immunomodulatory effects in the arthritic rat models,[9-11] although the exact dose-response relationship of such effect is not well-characterized in standardized animal models of inflammation. The present study was designed to evaluate the dose-response relationship of the orally administered boron, alone or as an adjuvant with dexamethasone in animal models of chronic and granulomatous inflammations.

METHODS

Wistar rats (150-200 g) of both sexes aged 8-10 weeks were purchased from the College of Medicine/Hawler Medical University, and housed in the animal house, School of Pharmacy, Faculty of Medical Sciences, University of Sulaimani during February to July 2014 in well ventilated plastic cages, maintained on normal conditions of temperature ($25\pm2°C$), humidity ($55\pm5\%$), and 12 hrs light/dark cycle. They were fed standard pellet chaw and had free access to water. The experimental protocol was approved by the Ethical Committee of the Faculty of Medical Sciences, University of Sulaimani. 66 rats were randomly allocated into different groups and treated as follow: negative control group includes six rats treated with vehicle only without induction of inflammation; the positive control group includes 12 rats subdivided into two groups (6 rats each), treated with vehicle only and with induction of chronic and granulomatous inflammation, respectively. The boron treated group includes 24 rats, allocated into four groups (6 rats each), and treated with two different doses of boron (disodium tetrahydroborate; Riedel-de Haen AG, Hannover, Germany) (3 and 6 mg/kg) orally with gavage tube, with induction of the two models of inflammation. The dexamethasone treated group includes 12 rats allocated into two subgroups (6 rats each) and treated with dexamethasone (TAD, Germany) (1 mg/kg) orally, with induction of the two types of inflammation. The dexamethasone-boron group includes 12 rats allocated into two subgroups (6 rats each), and treated with a combination of boron (3 mg/kg) and dexamethasone (1 mg/kg) orally with induction of inflammation.

In the first part of the study, the effect of boron in chronic inflammation was evaluated utilizing formaldehyde-induced paw edema.[12] Briefly, chronic inflammation was induced by injecting 0.1 ml of 2% formaldehyde subcutaneously in the plantar region of the right hind paw of ether-anesthetized rat. Both doses of boron (3 and 6 mg/kg), dexamethasone (1 mg/kg), and distilled water (0.2 ml/100 g) were given orally 30 mins prior to formaldehyde injection and continued for 7 consecutive days. Boron was given for 14 consecutive days; whereas, dexamethasone was given at the day of

inducing inflammation. The increase in paw thickness (edema) was measured using Digital Vernier, and presented as the mean increase in paw thickness (mm). The ability of drugs to suppress paw inflammation was expressed as a percentage of inhibition of paw edema calculated according to the following formula:

Percentage of inhibition (%)=$(C–T)/C \times 100$

In the second part, the effect of boron in granulomatous inflammation was evaluated utilizing cotton pellets-induced granuloma.[13] In this model, four sterile cotton pellets (10 ± 1 mg) were implanted subcutaneously into the ventral region of each rat under light ether anesthesia. The treatment pattern was similar to that mention in the 1st part. On 8th day after induction, the animals were anesthetized, and the pellets together with the granuloma tissues were carefully removed and made free from extraneous tissues. The wet pellets were weighed for determination of wet weight then dried at 60°C until a constant weight was obtained, and the dried pellets were weighed again to calculate the weights of exudate and granulation tissue. The percent inhibition of exudate and granuloma tissue formation was determined utilizing the following formula:

$$\text{Exudate inhibition (\%)}= \left(1 - \frac{\text{Weight of exudate in mg of treated group of rats}}{\text{Weight of exudate in mg of control group of rats}}\right) \times 100$$

$$\text{Granuloma inhibition (\%)}= \left(1 - \frac{\text{Weight of granulama in mg of treated group of rats}}{\text{Weight of granulama in mg of control group of rats}}\right) \times 100$$

Five milliliters of heart blood was drawn from each rat, and left to clot for 20 mins at room temperature. Serum was separated by centrifugation at 3000 rpm for approximately 20 mins, then stored at $-20°C$ unless immediately analyzed. Serum levels of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and high sensitivity C-reactive protein (hs-CRP) were analyzed using ready-made enzyme-linked immunosorbent assay kits according to the specifications of the manufacturer (YH Bioresearch laboratory, Shanghai, China).

All the results were expressed as SEM. The data were analyzed by using GraphPad Prism 5.1 software (Graph Pad Software Inc., San Diego, CA, USA). Unpaired *t*-test and one-way ANOVA followed by Bonferroni's *post-hoc* test were utilized for statistical evaluation of the differences between the means. $p<0.05$ were considered statistically significant.

RESULTS

Table 1 shows that treatment with boron decreases significantly formation of paw edema ($p<0.05$) in dose-

dependent pattern compared with the control, with maximum effect achieved with 6.0 mg/kg of boron (46.5%). Meanwhile, 1.0 mg/kg dexamethasone significantly attenuates the increase in paw thickness compared to control (58.8%). Boron (3.0 mg/kg) in combination with dexamethasone (1.0 mg/kg) results in 66.3% inhibition of paw edema, which was significantly higher than the effects produced by boron alone.

In Table 2, the data clearly shows that treatment with boron alone significantly decreases formation of inflammatory exudate, in a dose-dependent pattern, compared to control, with the maximum percentage of inhibition produced by the dose 6.0 mg/kg of boron (23%). Meanwhile, administration of 1.0 mg/kg of dexamethasone significantly decreases the exudate formation compared to control, reaching the maximum effect of 31%. Boron (3.0 mg/kg) in combination with dexamethasone (1.0 mg/kg) results in 36% decrease in exudate formation, which was significantly higher than all the effects produced by different doses of boron alone or dexamethasone alone (Table 2). Moreover, boron significantly decreases the formation of granuloma, in a dose-dependent pattern, compared with control, with the maximum effect produced by boron (38%). Meanwhile, 1.0 mg/kg dexamethasone attenuates significantly the formation of granuloma compared with control (59%). Boron (3.0 mg/kg) in combination with dexamethasone (1.0 mg/kg) results in 63% decrease in the formation of granuloma, which was significantly higher than all

the effects produced by the two doses of boron when administered alone (Table 2).

In the chronic inflammation model, Figure 1 shows that treatment with boron (3.0 mg/kg) significantly reduces serum TNF-α level, compared with controls. Meanwhile, 6.0 mg/kg produces a greater reduction in TNF-α level in challenged rats, which was nearly comparable to the effect of dexamethasone alone. Moreover, the highest degree of serum TNF-α level suppression was achieved by co-administration of boron (3.0 mg/kg) with dexamethasone (1.0 mg/kg). In Figure 2, both doses of boron significantly decreased serum IL-1β level after challenge with formalin (p<0.05), with maximum effect achieved with 6 mg/kg dose, which was approximately equivalent to that produced by dexamethasone. Meanwhile, the highest degree of IL-1β suppression was obtained by the co-administration of boron with dexamethasone. The results presented in Figure 3 shows that serum hs-CRP was significantly elevated in the formalin-challenged rats compared with negative control, and treatment with 6 mg/kg boron, 1 mg/kg dexamethasone and their combination significantly decreased serum hs-CRP levels in challenged rats, with maximum effect produced by the combination approach.

In the model of cotton-induced granuloma, both doses of boron attenuated TNF-α production compared with a positive control group (p<0.05), with greater effect reported with 6.0 mg/kg dose. The highest level of reduction in

Table 1: Effects of different doses of boron alone or adjuvant with dexamethasone on paw edema formation in formalin-induced chronic inflammation in rats.

Treatment groups	Paw thickness (mm) zero time	Paw thickness (mm) after 7 days	Δ thickness (mm) after 7 days	Inhibition of edema (%)
Control	4.5±0.13	7.7±0.21*	3.2±0.16[a]	-
Dexamethasone (1 mg/kg)	4.4±0.10	5.7±0.08*	1.3±0.16[b]	59.0±4.5[a]
Boron (3 mg/kg)	3.7±0.10	5.8±0.10*	2.1±0.16[c]	35.0±5.6[b]
Boron (6 mg/kg)	3.7±0.10	4.5±0.11*	1.7±0.17[b,c]	47.0±5.3[a,b]
Boron 3 mg/kg+ dexamethasone 1 mg/kg	3.4±0.09	5.4±0.20*	1.1±0.06[b,d]	66.0±3.4[a,c]

Values are presented as mean±SEM; n=6 rats in each group; *Significantly different compared with zero-time values (p<0.05) within the same group, using paired *t*-test; values with different superscripts (a, b, c, d) among different groups are significantly different (p<0.05), using ANOVA and *post-hoc* test, SEM: Standard error of mean

Table 2: Effects of different doses of boron alone, and its combination with dexamethasone on exudate and granuloma formation in cotton pellet-induced granuloma in rats.

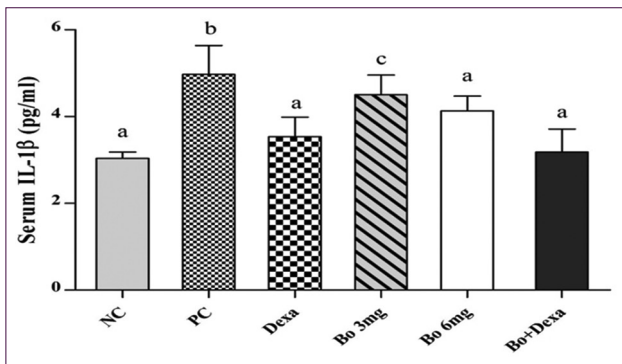| Treatment groups	Exudate (mg)	Inhibition of exudate (%)	Granuloma (mg)	Inhibition of granuloma (%)
Control	107.7±5.6[a]	-	46.0±4.1[a]	-
Dexamethasone (1 mg/kg)	74.8±4.4[b]	31.0	19.0±1.1[b]	59.0
Boron (3 mg/kg)	98.3±3.7[a]	8.0	33.7±2.6[c]	27.0
Boron (6 mg/kg)	83.2±5.6[b]	23.0	28.3±1.8[d]	38.0
Boron 3 mg/kg+dexamethasone 1 mg/kg	69.0±3.2[b]	36.0	16.8±0.8[b]	63.0

Values are presented as mean±SEM; n=6 rats in each group; values with different superscripts (a, b) among different groups are significantly different (p<0.05), using ANOVA and *post-hoc* test, SEM: Standard error of mean
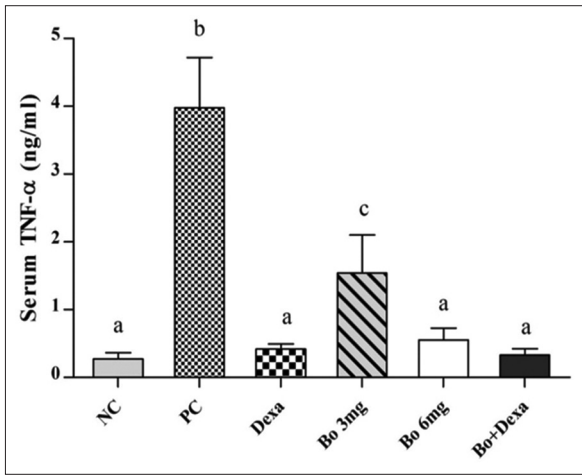
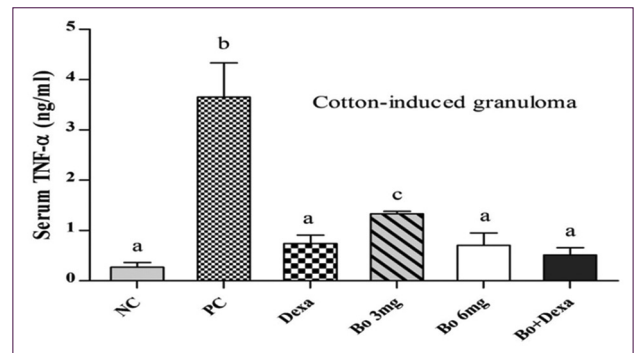**Figure 1: Effects of boron (3 and 6 mg/kg), dexamethasone (1 mg/kg) and their combination, on serum tumor necrosis factor-α levels in rat's model of formalin-induced chronic inflammation; number of rats = 6 in each group; NC: Negative control; PC: Positive control; values with non-identical letters (a, b, c) are significantly different using ANOVA and *post-hoc* test (p<0.05).**

Figure 2: Effects of boron (3 and 6 mg/kg), dexamethasone (1 mg/kg) and their combination on serum interleukin-1β levels in rat's model of formalin-induced chronic inflammation; number of rats=6 in each group; NC: Negative control; PC: Positive control; values with non-identical letters (a, b, c) are significantly different using ANOVA and *post-hoc* test (p<0.05).
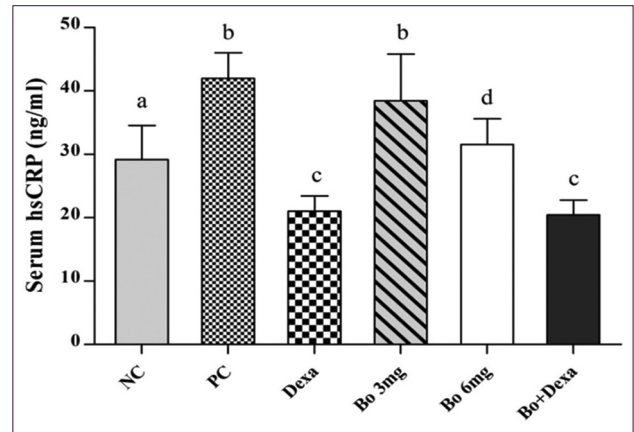
Figure 3: Effects of boron (3 and 6 mg/kg), dexamethasone (1 mg/kg) and their combination on serum high sensitivity C-reactive protein levels in rat's model of formalin-induced chronic inflammation; number of rats = 6 in each group; NC: Negative control; PC: Positive control; values with non-identical letters (a, b, c, d) are significantly different using ANOVA and *post-hoc* test (p<0.05).

Figure 4: Effects of boron (3 and 6 mg/kg), dexamethasone (1 mg/kg) and their combination on serum tumor necrosis factor-α levels in rat's model of cotton-induced granuloma; number of rats = 6 in each group; NC: Negative control; PC: Positive control; values with non-identical letters (a, b, c) are significantly different using ANOVA and *post-hoc* test (p<0.05).

serum TNF-α was achieved by the co-administration of dexamethasone with boron (Figure 4). Moreover, boron (6.0 mg/kg) significantly reduces serum IL-1β compared with the positive control group, while the 3.0 mg/kg dose does not show such effect. This effect was comparable to that produced by dexamethasone. Meanwhile, the combination approach produces the greatest inhibition in serum level of IL-1β (Figure 5). Regarding the effects on hs-CRP in granuloma model, both doses of boron significantly attenuate the elevation in serum hs-CRP level, compared with the positive control group. However, this effect was not dose-dependent, where both produced comparable effects in this regard (p>0.05). Moreover, although the combination of boron with dexamethasone produced a highest reduction in serum hs-CRP level, it was

not significantly different compared with other treatment approaches (Figure 6).

DISCUSSION

The possibility of decreasing inflammatory processes through daily administration of trace elements enriched food with therapeutic properties and low side effects is an attractive alternative to medical therapy.[14] A class of boron-containing antibacterial agents (borinic acid picolinate esters) was previously reported,[15] and a related antibacterial agent was prepared, which has additional activity against pro-inflammatory cytokines.[16] Such combination of activities is ideal for the treatment of topical infections with inflammatory consequences.
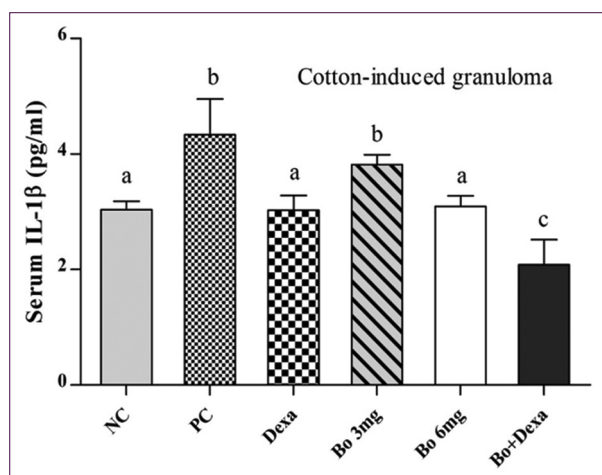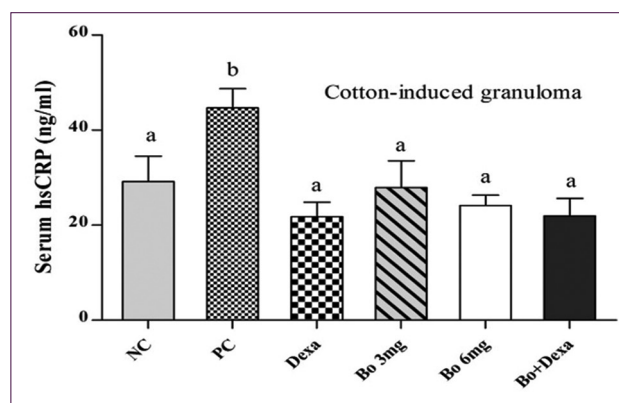
Figure 5: Effects of boron (3 and 6 mg/kg), dexamethasone (1 mg/kg) and their combination on serum interleukin-1β levels in rat's model of cotton-induced granuloma; number of rats = 6 in each group; NC: Negative control; PC: Positive control; values with non-identical letters (a, b, c) are significantly different using ANOVA and *post-hoc* test (p<0.05).

Figure 6: Effects of boron (3 and 6 mg/kg), dexamethasone (1 mg/kg) and their combination on serum high sensitivity C-reactive protein levels in rat's model of formalin-induced granuloma; number of rats = 6 in each group; NC: Negative control; PC: Positive control; values with non-identical letters (a, b) are significantly different using ANOVA and *post-hoc* test (p<0.05).

Accordingly, topical use of boron-containing preparations has been one of the options,[17] and two boron-containing phosphodiesterase-4 inhibitors have been developed as anti-inflammatory agents and clinically evaluated in psoriasis and atopic dermatitis.[18]

In the present study, the utilized models to induce chronic and granulomatous inflammation are widely accepted as sensitive and reliable tools to evaluate anti-inflammatory agents.[19] The presented data indicates that both doses of boron produced significant anti-inflammatory activity compared to control in a dose-dependent pattern, and its use as an adjuvant with dexamethasone seems to be the best approach to achieve highest anti-inflammatory activity compared to the other approaches. This might be attributed to the effects of both agents on the same or alternative pathways through which they thought to produce their anti-inflammatory activity. Although the results of the present study are consistent with many previously reported ones, the dose-response relationship can be considered as a new insight in this regard. Nielsen demonstrates the role of boron in human health, referencing the positive effects in bone, brain, inflammation, and hormone function.[20] Moreover, Newnham reveals the anti-arthritic effect of boric acid in animals and some forms of arthritis in humans.[21]

In the present study, boron significantly attenuates the increase in inflammatory reactions in the model of formalin-induced inflammation, and can be suggested as an anti-proliferative and anti-arthritic agent. The present data were in tune with that reported by others, where pigs that consumed boron-supplemented diets showed a decreased inflammatory response to an intradermal injection of phytohemagglutinin.[22] The mechanism behind the ability of boron to reduce inflammation is unclear, though many ideas are suggested to explain such activity based on both experimental and clinical data. In this regard, Hunt and Idso reported that paw swelling was reduced in adjuvant-induced arthritic rats that received supplemental boron,[23] and hypothesized that boron may decrease the inflammatory response, due to attenuating the production of pro-inflammatory cytokines by the monocyte/macrophage lineage.

The anti-inflammatory effects of boron can be attributed to various mechanisms, including suppression of serine proteases released by inflammation-activated white blood cells, inhibition of leukotriene synthesis, reduction of reactive oxygen species generated during neutrophil's respiratory burst, suppression of T-cell activity and antibody concentrations.[24] Another possible explanation for the decreased inflammatory response in boron-pretreated rats might be related to the interference with the production of cytokines, specifically interferon-γ and TNF-α from monocytes and macrophages.[22] In the animal model of granuloma, both doses of boron possesses marked anti-inflammatory activity compared to controls. This effect could be attributed to the reduction in exudate and granuloma formation during the second phase of the inflammatory reaction. Although these results are clear within the limitations of the utilized method, previously reported data raises many doubts about the effect of boron in this regard, where dietary boron supplementation increases production of cytokines following stress, which indicates a role for boron in the immune system.[25] However, these data do not explain the reduction in localized inflammation following an antigen challenge in pigs.[22] Such discrepancy in the behavior of boron may be attributed to the variation in the doses and methods of administration followed during the experiments. Utilization of sensitive biochemical markers may give more evidence in this respect.

Moreover, the present data supports the approach of using a combination of boron with corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs) as adjuvant therapy for resistant cases of chronic inflammatory disorders like rheumatoid arthritis, which may enable reducing the doses of corticosteroids or NSAIDs, and decrease the chance of side effects. However, the exact mechanism behind the anti-inflammatory activity of boron remains incompletely revealed. The previous and currently presented data, which indicate decreased localized inflammatory response following boron supplementation cannot be explained only by decreased cytokine production due to boron supplementation.[26] Therefore, a mechanism beyond reduction of cytokine production by boron might explain the decreased local tissue swelling following an intradermal injection of irritant substances. Hunt and Idso suggested that the reduced inflammation in rats that received boron-supplemented diets can be explained on the bases of downregulating certain enzymes involved in the respiratory burst cascade,[23] associated with a decrease in the production of reactive oxygen species.

CONCLUSION

Boron, in a dose-dependent pattern, effectively suppresses formaldehyde-induced chronic inflammation, and cotton pellet-induced granuloma in rats when used alone or as adjuvant with dexamethasone. It may be considered as a potential treatment for chronic inflammatory conditions.

ACKNOWLEDGMENTS

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