

## REVIEW ARTICLE

# Drug Overdose-Induced Coma Blisters: Pathophysiology and Clinical and Forensic Diagnosis

Ricardo J. Dinis-Oliveira<sup>1,2,3,\*</sup>

<sup>1</sup>IINFACTS - Institute of Research and Advanced Training in Health Sciences and Technologies, Department of Sciences, University Institute of Health Sciences (IUCS), CESPU, CRL, Gandra, Portugal; <sup>2</sup>UCIBIO, REQUIMTE, Laboratory of Toxicology, Department of Biological Sciences, Faculty of Pharmacy, University of Porto, Porto, Portugal; <sup>3</sup>Department of Public Health and Forensic Sciences, and Medical Education, Faculty of Medicine, University of Porto, Porto, Portugal

---

## ARTICLE HISTORY

Received: February 13, 2018  
Revised: June 26, 2018  
Accepted: July 19, 2018

DOI:  
10.2174/1874473711666180730102343

**Abstract: Background:** Coma blisters or coma *bullae* are bullous lesions that have been associated with cases of drug overdose-induced coma. Previous history of suicide attempt by administering benzodiazepines, barbiturates, ethanol, antipsychotics, antidepressants or opioids have been particularly implicated. Patients may present also painful deep skin and soft tissue involvement, edema and functional impairment. The pathophysiology remains unknown and lesions are usually self-limited and typically resolve without scarring.

**Objective:** This work aims to fully review the state of the art regarding the causes pathophysiology, diagnosis and treatment of drug overdose-induced coma blisters.

**Conclusion:** Coma blisters are a benign, self-limiting condition that should be suspected in patients who develop pressure blisters several hours after an altered state of consciousness.

**Keywords:** Coma blisters, drug overdose, diagnosis, histopathology, treatment, pathophysiology.

## 1. INTRODUCTION

Coma blisters or coma *bullae* were firstly described in 1812, when Dominique Jean Larrey (the Napoleon's surgeon) noticed blisters in soldiers of the French Revolution who had been comatose from carbon monoxide intoxication [1]. Blisters were then described in the comatose patient due to barbiturates [2], and since then have been linked to overdose by several drugs, namely psychoactive ones, such as benzodiazepines, barbiturates, antidepressants, antipsychotics, ethanol or opioids. Due to the historical association to barbiturates overdose, coma blisters have also been colloquially referred to as "barb burns" or "barb blisters". Coma blisters have been reported in 5% of adult patients hospitalized for drug-induced coma [3, 4]. They consist of tense and flaccid blisters more frequently developed in pressure and ischemic areas (e.g., trunk and distally in the limbs) of patients with impaired mental status, the adjacent skin being typically spared. They commonly develop 48 to 72 hours after the onset of unconsciousness and the eruptions are usually self-limited in 1 to 2 weeks [5]. While it has been suggested that some toxic effect of drugs may play a role, the relation between coma blisters and any specific drug it has not been proven [6, 7].

The prompt recognition of coma blisters with pain is important since raised interstitial pressures can cause irreversible nerve and muscle damage [8]. Moreover, from a clinical and forensic perspective good knowledge of the signs related

to acute and chronic intoxications represents an important step of suspicion to orientate further toxicological analysis [9-14]. Indeed, for some authors, coma blisters with deep soft tissue are hardly described in the literature and probably under-recognized or even misdiagnosed as cellulitis or other disorders [8] and most literature data is focused on the description of isolated case reports. Therefore, this work aims to perform a fully integrated review the state of the art regarding cause, pathophysiology, diagnosis and treatment of drug overdose-induced coma blisters. Additionally, non-drug reported causes were also reviewed in attempt to offer further insights on differential diagnosis. Finally, it is important to remember as for all intoxications, coma blisters are not specific pathognomonic signs of drug overdose which means that these characteristic lesions should be further confirmed by toxicological analysis.

## 2. METHODOLOGY

An exhaustive search was carried out in PubMed (U.S. National Library of Medicine) without a limiting period, concerning coma blisters and epidemiology, pathophysiology, causes, diagnosis and treatment. Keywords such as coma blisters or coma *bullae*, overdose, barbiturates, differential diagnosis, histopathology and treatment were searched in articles written in English, German, French, Spanish and Portuguese. Furthermore, retrieved journal articles as well as books were also reviewed for possible additional publications related to this topic and authors were contacted in order to obtain additional images with better artwork quality.

---

\*Address correspondence to this author at the Department of Sciences, University Institute of Health Sciences (IUCS)-CESPU, Rua Central de Gandra, 1317, 4585-116 Gandra, PRD, Portugal; Tel: +351 224 157 216; Fax: +351 224 157 102; E-mail: [ricardinis@sapo.pt](mailto:ricardinis@sapo.pt)

### 3. EPIDEMIOLOGY AND CLINICAL FEATURES

Coma blisters has been mainly associated with overdose of drugs, namely nervous system depressants, such as barbiturates, benzodiazepines (e.g., nitrazepam), tricyclic antidepressants (e.g., amitriptyline), antipsychotics (e.g., quetiapine), anticonvulsants (e.g., valproic acid), opioids (e.g., methadone, heroin), glutethimide, theophylline and ethanol [11, 15-17]. Neurological disorders, such as viral meningoencephalitis, cerebrovascular disease, strokes, and cranioencephalic trauma, and metabolic disorders, such as hyperkalemia, hypoglycemia, and diabetic ketoacidosis, and pneumonia have also been implicated [15, 18-21]. Moreover, coma blisters, have also been described in patients without an altered state of conscience, in particular in cases of long immobilization or Wegener granulomatosis [15, 18, 19]. Comparatively to adults, very few cases of drug overdose-induced coma blisters have been reported in children [22, 23].

Most reports describe patients with tense fluid-filled bullae after the appearance of an erythematous plaque not forming exclusively in pressure-dependent sites. The lesions may be variable in size ranging from 5 to 4 cm and occasionally appear hemorrhagic [24]. In 1952, the appearance of coma blisters was reported in 4% of a series of 501 patients intoxicated by barbiturates [25]. In another study, blisters were found in 6.5% of barbiturate overdoses [26]. In opposition, Keng *et al.* [17] presented a case of a noncomatose, nonimmobilized patient who developed systemic bullous lesions after an acute but non-toxic ingestion of oral phenobarbital (Fig. 1A and B). Vazquez-Osorio [27] presented a case of a 24-year-old woman with a history of a personality disorder and occasional consumption of cocaine and amphetamines who was found unconscious in her home after administration of multiple tablets from her regular medication such as topiramate, duloxetine, quetiapine, and clorazepate. On arrival at the emergency room, she had a low level of consciousness (score 6 on the Glasgow Coma Scale), pale skin, and reactive mydriatic pupils. Partial improvement (Glasgow Coma Scale 10) was observed following physical stimulation, and the patient was treated with oxygen, fluid therapy, gastric lavage, and activated charcoal. During her first 24 hours in hospital, the patient developed asymptomatic skin lesions located mainly on pressure points of bony prominences of the metacarpophalangeal joints on the right hand, right hip, and left knee (Fig. 1C and D). The physical examination showed tense clear fluid-filled blisters on well-delimited erythematous plaques. A 49-year-old man was admitted to the emergency room with progressive loss of consciousness after an attempted suicide with tricyclic antidepressant, opioids, and benzodiazepine overdose [8].

Several cases have been associated with amitriptyline administration. Herschthal and Robinson [28] described coma blisters in a 23-year-old female after ingestion of amitriptyline and clorazepate dipotassium. Reilly and Harrington [29] reported coma blisters in a 55-year-old man after multidrug ingestion, including amitriptyline. In a 37-year-old man, amitriptyline was also implicated in full-thickness skin necrosis requiring skin grafting [30]. Maguiness *et al.* [31] reported erythematous plaques and several tense coma blisters associated with peripheral neuropathy in a 26-year-old female after overdose with amitriptyline. Authors suggested that amitriptyline causes a dose-dependent de-

crease in transcellular resistance and increased endothelial cell permeability, which may increase susceptibility to skin blistering [31, 32].

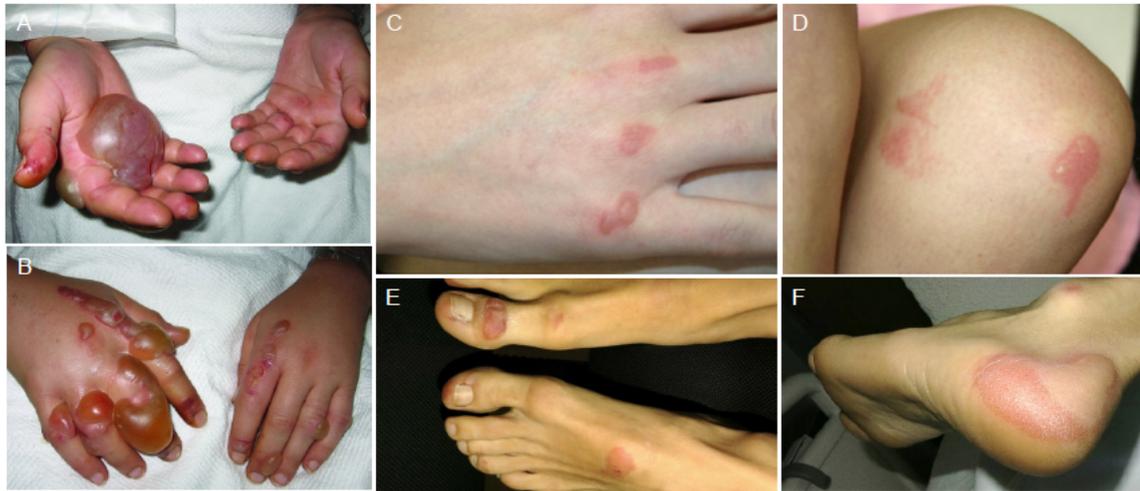
Several other drugs-related etiologies have been described in literature. Tsokos and Sperhake [33] reported a fatal case resulting from theophylline overdose in a 44-year-old Caucasian woman. External examination revealed two tense cutaneous blisters at the ulnar surface of the left forearm containing reddish fluid. In 3 children, the onset of bullous lesions was related to drug administration of clobazam, valproic acid, clonazepam, vigabatrin and levetiracetam [34, 35]. A 27-year-old female suffered a prolonged coma after suicide attempt with a quetiapine overdose [36]. The patient had multiple dermatologic manifestations attributed to coma, namely vesicles on his right ankle and a firm, erythematous plaque and bullae on his right thigh [36]. A quadriplegic 24-year-old female was admitted in the emergency room with respiratory failure due to pneumonia. She developed multiple blisters on pressure and non-pressure bearing areas of the right forearm and hand. Skin biopsy revealed eccrine gland degeneration consistent with coma blisters and it was suggested that hypoxemia contributed to blisters development [24].

### 4. PATHOPHYSIOLOGY

Multiple factors have been implicated in the pathogenesis of coma blisters, including local pressure or friction, generalized hypoxia and tissue ischemia, direct toxicity due to drugs excreted in sweat on the skin and eccrine glands, immune mechanisms, and vasomotor changes in comatose states, but the exact etiology of the blisters remains controversial [18, 22]. It has been suggested that tissue injury is proportional to the time and amount of pressure-induced local ischemia. Since it is recognized that the eccrine gland is a metabolically active unit they are particularly more susceptible to ischemic necrosis [5]. Therefore, the histological observation of necrotic eccrine glands with minimal or absent inflammation is a characteristic finding of coma blisters [4]. Necrosis can also be present in the epithelium of pilosebaceous follicles. In the setting of uninterrupted pressure injury, arterial hypotension related to shock or vasoactive drugs may also play a role [18].

### 5. DIAGNOSIS

Biopsy followed by histopathological analysis has been considered the hallmark of coma blisters diagnosis. The histologic features, were firstly described in 1969 by Leavell [37]. The claimed vascular damage observed in drug overdose-induced coma blisters is probably a consequence rather than a cause of the blisters. Furthermore, the absence of an epidermal infiltrate and the presence of thrombi in the dermal vessels are mainly observed in nondrug-induced coma blisters [4]. The histopathologic examination evidenced typically subepidermal or intraepidermal blisters with foci of reepithelialization and eccrine gland necrosis, mainly affecting the secretory portion and with periglandular infiltration of neutrophils [27]. The secretory coils and ducts of the eccrine glands may present a granular eosinophilic cytoplasm, ghost nuclei, and irregular membranes. Additional findings included dermal, perivascular, and periadnexal infiltrates,



**Fig. (1).** Coma blisters after drug overdose. A and B – Tense and fluid-filled blisters in the palmar surface and dorsum of each finger; C - Tense clear fluid-filled blisters on well-delimited erythematous plaques on the metacarpophalangeal joints; D - Similar lesions on the left knee with an artefactual morphology; E - Hemorrhagic tense blisters over the left heel; F - Flaccid blisters over the toes. A and B reprinted with permission from [17], C and D from [27], and E and F from [8].

which were predominantly neutrophilic, together with foci of fibrinoid necrosis in the walls of the small dermal capillaries and neutrophilic infiltration of the walls [27]. However, the absence of necrosis in eccrine glands does not necessarily rule out a diagnosis of coma blisters. Other possible findings are neutrophilic perivascular infiltrates, necrosis of dermal or subcutaneous tissue or epidermal appendages, focal fibrinoid necrosis of the walls of small capillaries and arterioles, and thrombi in the lumen of dermal vascular structures [4].

Ruiz-Rivero *et al.* [8] described a sudden and rapid onset of hemorrhagic and serous blisters symmetrically distributed over the legs, heels, dorsum of toes, and back of the hands (Fig. 1E and F). Punch biopsy was taken from a pretibial lesion. Histological findings included necrosis of sweat glands and sweat duct keratinocytes, as well as a focal eosinophilic thickening of the basement membrane. After recovering consciousness, approximately 96 hours after admission, he also complained of pain in the lateral side of his right leg. On examination, the leg was edematous and slightly erythematous, which was interpreted as bacterial cellulitis.

Biopsies analysis obtained from the periphery of two of the large bullae showed extensive epidermal necrosis of the squamous cell layers with no evidence of basal regeneration, significant necrosis of follicular structures and evidence of vasculitis and neutrophilic exudate in the infundibulum [31]. Histologic examination of the skin blisters also showed that the epidermal layer is separated off the dermis, thus creating a bullous lesion filled with amorphous material. The eccrine sweat gland coil showed eosinophilic necrosis of and basophilia of the nuclei [33]. Analysis of a skin biopsy obtained from the blister edge of a 18-year-old female, demonstrated varying degrees of epidermal necrosis, with areas of full thickness necrosis and loss of nuclei and the eccrine coils in the deep dermis showed necrosis with loss of nuclei and a pink homogenized appearance [22].

Direct immunofluorescence studies of coma blisters have shown patched intercellular staining for immunoglobulin (Ig) G, IgA, and C3, together with IgG, IgM, and C3 deposits in dermal vessel walls and epidermal keratinocytes. However,

the results interpretation remains controversial, particularly due to a possible nonspecific interaction rather than a direct immune-mediated pathogenic mechanism [4, 6]. A 45-year-old woman developed coma blisters at six distinct anatomic sites after phenobarbital poisoning, associated with other central nervous system depressants (*i.e.*, clonazepam, promethazine, oxcarbazepine and quetiapine) [38]. Direct immunofluorescence was strongly positive for IgG in superficial blood vessel walls but negative for IgM, IgA, C3 and C1q [38].

An interesting work [39] performed analysis of the skin lesions in order to understand the pathogenesis of the coma blisters in a forensic autopsy after caffeine overdose. Skin lesions exhibited necrotic keratinocytes, thin epidermis in some areas, degeneration of eccrine sweat glands and a non-clear inflammatory cells infiltration. Immunohistochemistry analysis on each skin lesion against several targets revealed positivity for CD45RO, CK-L and M30. Authors suggested that these biomarkers may be useful in observing the sweat gland degeneration in coma blisters. They also concluded that apoptosis might be implicated in coma blisters pathophysiology and sweat gland degenerations due to M30 immunoreactivity [39]. Indeed, during epithelial cell apoptosis, intermediate filaments are reorganized and keratin 18 is cleaved by caspases to release M30, which is one of the most specific and earliest detected biomarkers of apoptosis [40]. This study also offered a tool for differential diagnosis for *postmortem* putrefaction artifacts typically observed in forensic autopsy cases [39]. Moreover, since sweat gland degenerations were only registered in coma blister areas, authors suggested that sweat gland degeneration was considered as specific finding for coma blister.

Differential diagnosis may include autoimmune bullous diseases (*e.g.*, pemphigoids, epidermolysis bullosa), bullous diabeticorum, bullous drug eruptions, retiform purpura, friction and postburn blisters [23, 41]. Moreover, coma blisters differ from pressure ulcers in several points and cannot be classified using the typical staging system graded from I to IV based on determining sequential layers of dermis and

subcutaneous injury [42]. An intraepidermal blister cavity just below the granular layer is seen in friction blisters, whereas a subepidermal split with sweat gland/follicular necrosis is characteristic of coma blisters.

The only treatment indicated is topical antibiotics to prevent secondary infections [19, 23, 27]. Other underlying diseases and comorbidities should also be monitored to improve the overall health, neurologic status, cardiopulmonary function, and tissue perfusion [22].

## CONCLUSION

Coma blisters are an interesting and rare condition, mainly described in adults. They occur both in the event of drug overdose and in nondrug-induced coma. Clinically, coma blisters are characterized by tense clear or hemorrhagic blisters that develop on erythematous-violaceous macules or plaques of varying size. The lesions typically appear within 24 hours of drugs overdose and within 48 to 72 hours of the loss of consciousness [24]. They primarily develop on pressure points, such as fingers and toes, elbows, knees, ankles, and heels, but formation in non-pressure bearing areas has also been described. They are self-limiting and heal within days or 1-2 weeks, without or residually causing scarring or atrophy [43, 44]. Anoxia is the most reported explanation. Although a diagnosis can be established on clinical signs and symptoms only, a histopathologic study is claimed to be the hallmark specially to rule out other blistering dermatoses [6]. Histologically, these lesions have been characterized by the pathognomonic eccrine sweat gland necrosis which underlies epidermal necrosis and subepidermal blisters; however, the absence of sweat duct necrosis does not exclude the coma blisters [43]. There is also usually a mild to moderate dermal inflammatory infiltrate with arteriolar damage and fibrin deposition [4].

In conclusion, coma blisters are a benign, self-limiting condition that should be suspected in patients who develop pressure blisters several hours after an altered state of consciousness. The etiopathogenesis remains speculative, in part due to the paucity of available histopathology analysis. Moreover, since several studies report association of drugs, it is important to assure a careful prescription.

## CONSENT FOR PUBLICATION

Not applicable.

## CONFLICT OF INTEREST

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties. No writing assistance was utilized in the production of this manuscript.

## ACKNOWLEDGEMENTS

Ricardo Dinis-Oliveira acknowledges Fundação para a Ciência e a Tecnologia (FCT) for his Investigator Grant (IF/01147/2013).

## REFERENCES

- [1] Larrey DJ. Memoires de chirurgie militaire et campagnes. Smith and Buisson 1812; 3:13.
- [2] Villaret ML, Bith H, Desoille M. Ulcérations cutanées dues aux barbituriques. *Paris Med* 1932; 2: 340.
- [3] Wenzel, FG, Horn TD. Nonneoplastic disorders of the eccrine glands. *J Am Acad Dermatol* 1998; 38: 1-17.
- [4] Sanchez YE, Requena L, Simon P. Histopathology of cutaneous changes in drug-induced coma. *Am J Dermatopathol* 1993; 15: 208-16.
- [5] Rocha J, Pereira T, Ventura F, Pardal F, Brito C. Coma Blisters. *Case Rep Dermatol* 2009; 1: 66-70.
- [6] Branco MM, Capitani EM, Cintra ML, Hyslop S, Carvalho AC, Bucarechi F. Coma blisters after poisoning caused by central nervous system depressants: Case report including histopathological findings. *An Bras Dermatol* 2012; 87: 615-7.
- [7] Holden CE. Cutaneous bullae in coma due to poisoning. An association with deep seated ischaemic lesions of muscle. *Anaesthesia* 1977; 32: 554-5.
- [8] Ruiz-Rivero J, Pulido-Perez A, Suarez-Fernandez RM. Coma blisters with deep soft tissue involvement after drug overdose. *Int J Dermatol* 2017; 56: 881-3.
- [9] Dinis-Oliveira RJ, Caldas I, Carvalho F, Magalhaes T. Bruxism after 3,4-methylenedioxymethamphetamine (ecstasy) abuse. *Clin Toxicol (Phila)* 2010; 48: 863-4.
- [10] Dinis-Oliveira RJ, Carvalho F, Duarte JA, Proenca JB, Santos A, Magalhães T. Clinical and forensic signs related to cocaine abuse. *Curr Drug Abuse Rev* 2012; 5: 64-83.
- [11] Dinis-Oliveira RJ, Carvalho F, Moreira R, Duarte JA, Proenca JB, Santos A, Magalhães T. Clinical and forensic signs related to opioids abuse. *Curr Drug Abuse Rev* 2012; 5: 273-90.
- [12] Dinis-Oliveira RJ, Carvalho F, Moreira R, Proenca JB, Santos A, Duarte JA, Bastos ML, Magalhaes T. Clinical and forensic signs related to chemical burns: A mechanistic approach. *Burns* 2015; 41: 658-79.
- [13] Dinis-Oliveira RJ, Magalhães T, Moreira R, Proenca JB, Pontes H, Santos A, Duarte JA, Carvalho F. Clinical and forensic signs related to ethanol abuse: A mechanistic approach. *Toxicol Mech Methods* 2014; 24: 81-110.
- [14] Dinis-Oliveira RJ, Magalhães T, Queiros O, Proenca JB, Moreira R, de Lourdes BM, Carvalho, F. Signs and Related Mechanisms of Ethanol Hepatotoxicity. *Curr Drug Abuse Rev* 2015; 8: 86-103.
- [15] Dunn C, Held JL, Spitz J, Silvers DN, Grossman ME, Kohn SR. Coma blisters: report and review. *Cutis* 1990; 45: 423-6.
- [16] You MY, Yun SK, Ihm W. Bullae and sweat gland necrosis after an alcoholic deep slumber. *Cutis* 2002; 69: 265-8.
- [17] Keng M, Lagos M, Liepman MR, Trever K. Phenobarbital-induced bullous lesions in a non-comatose patient. *Psychiatry (Edgmont)* 2006; 3: 65-9.
- [18] Arndt KA, Mihm MC, Parrish JA. Bullae: a cutaneous sign of a variety of neurologic diseases. *J Invest Dermatol* 1973; 60: 312-20.
- [19] Piede J, Wallace E. Coma bullae: Associations beyond medications. *Mayo Clin Proc* 2011; 86: e5.
- [20] Mehregan DR, Daoud M, Rogers RS. 3<sup>rd</sup> Coma blisters in a patient with diabetic ketoacidosis. *J Am Acad Dermatol* 1992; 27: 269-70.
- [21] Chang KS, Su YJ. Coma blister in nontraumatic rhabdomyolysis. *Am J Emerg Med* 2016; 34: 1324.e1-2.
- [22] Chacon AH, Farooq U, Choudhary S, *et al*. Coma blisters in two postoperative patients. *Am J Emerg Med* 2013; 35: 381-4.
- [23] Bosco L, Schena D, Colato C, Biban P, Girolomoni G. Coma blisters in children: case report and review of the literature. *J Child Neurol* 2013; 28: 1677-80.
- [24] Agarwal A, Bansal M, Conner K. Coma blisters with hypoxemic respiratory failure. *Dermatol Online J* 2012; 18: 10.
- [25] Holten C. Cutaneous phenomena in acute barbiturate poisoning. *Acta Derm Venereol* 1952; 32: 162-8.
- [26] Beveridge GW, Lawson AA. Occurrence of bullous lesions in acute barbiturate intoxication. *BMJ* 1965; 1: 835-7.
- [27] Vazquez-Osorio I, Gonzalvo-Rodriguez P, Rodriguez-Diaz E. Coma Blisters after an Overdose of Central Nervous System Depressants. *Acta Dermosifiliogr* 2017; 108: 81-3.
- [28] Herschthal D, Robinson MJ. Blisters of the skin in coma induced by amitriptyline and clorazepate dipotassium. Report of a case with underlying sweat gland necrosis. *Arch Dermatol* 1979; 115: 499.

- [29] Reilly GD, Harrington CI. Positive immunofluorescence in bullous lesions in drug-induced coma. *Br J Dermatol* 1983; 109: 720.
- [30] Fogarty BJ, Khan K. Drug induced blistering and the plastic surgeon: a case of amitriptyline induced skin necrosis. *Burns* 1999; 25: 768-70.
- [31] Maguiness S, Guenther L, Shum D. Coma blisters, peripheral neuropathy, and amitriptyline overdose: A brief report. *J Cutan Med Surg* 2002; 6: 438-41.
- [32] Dahlin KL, Bohlin K, Strindlund J, Ryrfeldt A, Cotgreave IA. Amitriptyline-induced loss of tight junction integrity in a human endothelial-smooth muscle cell bi-layer model. *Toxicology* 1999; 136: 1-13.
- [33] Tsokos M, Sperhake JP. Coma blisters in a case of fatal theophylline intoxication. *Am J Forensic Med Pathol* 2002; 23: 292-4.
- [34] Bas A, Brown S, Kirkham N, Ramesh V, Leech S, Devlin A. Coma blisters in 2 children on anticonvulsant medication. *J Pediatr Neurol* 2009; 24: 1021-5.
- [35] Setterfield JF, Robinson R, MacDonald D, Calonje E. Coma-induced bullae and sweat gland necrosis following clobazam. *Clin Exp Dermatol* 2000; 25: 215-8.
- [36] Wiegand TJ, Gorodetsky RM, Peredy TR. Coma blisters in the setting of quetiapine overdose: case report and review of literature. *Asia Pac J Med Toxicol* 2013; 2: 153-6.
- [37] Leavell UW. Sweat gland necrosis in barbiturate poisoning. *Arch Dermatol* 1969; 100: 218-21.
- [38] Branco MM, Capitani EMD, Cintra ML, Hyslop S, Carvalho AC, Bucaretychi F. Coma blisters after poisoning caused by central nervous system depressants: Case report including histopathological findings. *An Bras Dermatol* 2012; 87: 615-7.
- [39] Kashiwagi M, Ishigami A, Hara K, *et al.* Immunohistochemical investigation of the coma blister and its pathogenesis. *J Med Invest* 2013; 60: 256-61.
- [40] Caulin C, Salvesen GS, Oshima RG. Caspase cleavage of keratin 18 and reorganization of intermediate filaments during epithelial cell apoptosis. *J Cell Biol* 1997; 138: 1379-94.
- [41] Melrose E, Laageide L, Mutgi K, Stone MS, Wanat KA. Pressure-induced necrosis can mimic retiform purpura. *JAAD Case Rep* 2018; 4: 365-7.
- [42] Ankrom MA, Bennett RG, Sprigle S, *et al.* Pressure-related deep tissue injury under intact skin and the current pressure ulcer staging systems. *Adv Skin Wound Care* 2005; 18: 35-42.
- [43] Varma AJ, Fisher BK, Sarin MK. Diazepam-induced coma with bullae and eccrine sweat gland necrosis. *Ann Intern Med* 1977; 137: 1207-10.
- [44] Waring WS, Sandilands EA. Coma blisters. *Clin Toxicol (Phila)* 200; 45: 808-9.