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Injury due to extravasation of thiopental and propofol: Risks/effects of local cooling/warming in rats

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ABSTRACT

Inadvertent leakage of medications with vesicant properties can cause severe necrosis in tissue, which can have devastating long-term consequences. The aim of this study was to evaluate the extent of extravasation injury induced by thiopental and propofol, and the effects of cooling or warming of local tissue on extravasation injury at macroscopic and histopathologic levels. Rats were administered intradermally thiopental (2.5 mg/100 μL) or propofol (1.0 mg/100 μL). Rats were assigned randomly to three groups: control (no treatment), cooling and warming. Local cooling (18–20 °C) or warming (40–42 °C) was applied for 3 h immediately after agent injection. Lesion sizes (erythema, induration, ulceration, necrosis) were monitored after agent injection. Histopathology was evaluated in skin biopsies taken 24 h after agent injection. Thiopental injection induced severe skin injury with necrosis. Peak lesions developed within 24 h and healed gradually 18–27 days after extravasation. Propofol induced inflammation but no ulceration, and lesions healed within 1–2 days. Local cooling reduced thiopental- and propofol-induced extravasation injuries but warming strongly exacerbated the skin lesions (e.g., degeneration, necrosis) induced by extravasation of thiopental and propofol. Thiopental can be classified as a "vesicant" that causes tissue necrosis and propofol can be classified as an "irritant". Local cooling protects (at least in part) against skin disorders induced by thiopental and propofol, whereas warming is harmful.

1. Introduction

Accidental leakage of certain medications into the body from an intravenous drip is not uncommon. Inadvertent leakage of medications with vesicant properties can cause severe necrosis in tissue, which can have devastating long-term consequences. Most instances of extravasation are attributed to cytotoxic agents, and the prevalence has been reported to be 0.1–6% [1,2]. In addition, several non-cytotoxic agents have been reported to possess vesicant properties due to their high osmolarity, extremely acidic or basic pH, and vasoconstrictive activity [3]. Several guidelines for overall management of extravasation have suggested that recognition of potential risks for each agent is important so that clinicians can manage extravasation depending on the severity of

such risks [4,5]. Intravenous cytotoxic agents can be classified into three categories according to the extent of damage from extravasation: vesicants, irritants, and non-tissue-damaging agents [1,2,4]. Vesicants can cause tissue necrosis even at small volumes of extravasation because they are inherently toxic to cells. Irritants can cause an inflammatory reaction (but not necrosis) at the extravasation site. Non-tissue-damaging agents do not damage tissue at all.

Thiopental and propofol are used for the induction and maintenance of anesthesia. Extravasation of these agents is common because anaesthetized patients cannot indicate pain during injection [6]. Risk of extravasation injury is increased because propofol is administered forcefully using automated syringe drivers. Several case reports from 1961 through to 2014 have highlighted extravasation by thiopental or propofol [3]. It is well known that thiopental can act as a vesicant [7] and propofol can act as an irritant [8–11]. However, few reports have shown the vesicant effects of propofol [12–14]. Thus, the risk of skin lesions induced by propofol extravasation is understood incompletely because data

are limited to a few case reports. Clinicians manage extravasation injuries according to the potential risks of agents. Hence, classification of non-cytotoxic agents into the three categories described above (as well as cytotoxic agents) depending on their toxicity would be useful.

Prompt interdisciplinary management of tissue damage induced by extravasated agents is important for successful therapy. Several reports have shown that stopping the drug infusion as well as surgical excision, thermal application and/or pharmacologic interventions aid management of injury due to extravasation of agents [4,5]. Cooling or warming of local tissue are major supportive measures to reduce skin lesions induced by certain agents [1,3,4,15]. According to one overview of extravasation management [16], hospitals should ensure the availability of "extravasation kits containing cold–hot packs" at the treatment unit. However, there is little scientific basis for the effects of poultices on skin lesions. With regard to management of thiopental extravasation, warming is recommended by the manufacturer, though there is no evidence to indicate therapeutic effects. With respect to management of propofol extravasation, only one report has shown that cooling reduces pain [17]. Thus, the usefulness of cooling or warming of local tissue to manage injuries induced by extravasation of thiopental or propofol is not known.

In the present study, we first evaluated the extent of extravasation injuries induced by thiopental or propofol and classified these agents (as well as cytotoxic agents) on the basis of macroscopic and histopathologic evaluations of skin damage. Next, the effects of local cooling or warming on extravasation injury were evaluated to provide a comprehensive view of management strategies for extravasation of thiopental and propofol.

2. Materials and methods

2.1. Animals

All experiments were carried out in accordance with the *Guide for Animal Experimentation from the Committee of Research Facilities for Laboratory Animal Sciences of Hiroshima University* (permit number: A15-31).

Thirty-three male Wistar albino rats (8 weeks; body weight, 250–270 g) were obtained from Japan SLC, Inc. (Shizuoka, Japan). Rats were housed in individual cages in a temperature-controlled room at 23 °C on a 12-h light–dark cycle. They were fed a standard laboratory diet (MF, Oriental Yeast Company, Tokyo, Japan) and water *ad libitum* for > 1 week before experimentation.

2.2. Extravasation models

Rats were anesthetized with pentobarbital (40 mg/kg, i.p.). According to a previous report [18], the hair on the back of rats was shaved with an electrical clipper (Thrive 2100; Daito Electric Machine Industry Co. Ltd., Osaka, Japan). Sodium thiopental (Ravonal®; Tanabe–Mitsubishi, Osaka, Japan) was dissolved at 2.5 mg/100 μL in water for injection according to manufacturer instructions. Twenty-four hours after hair removal, rats with no wounds were injected intradermally (i.d.) with a solution of thiopental or propofol (1.0 mg/100 μL of Diprivan®; AstraZeneca, Osaka, Japan) at 100 μL (the minimum volume at which lesions can be observed macroscopically). As a negative control group, physiologic (0.9%) saline was injected (i.d.) at 100 μL as well as thiopental and propofol. Intradermal injections were undertaken after grabbing dorsal skin using a 26-G needle at the center of a hair-free site 7 cm from the ear. Two injections were made on the axisymmetric dorsal side of each rat. Right-side lesions were monitored until the injury healed completely. Left-side lesions were punch-biopsied

(using a dermal punch) 24 h after intradermal injection for histopathologic evaluation under anesthesia with pentobarbital.

2.3. Cooling and warming of local tissue

Rats that had undergone intradermal injection of thiopental or propofol were assigned randomly to three experimental groups of 5 rats each: no treatment (control); cooling (treatment with a cold pack); warming (treatment with a hot pack). Cooling and warming of local tissue were done for 3 h immediately after intradermal injection using cold or hot packs (3M HealthCare, Tokyo, Japan), respectively [19]. Three rats were assigned to a group in which saline was injected via the intradermal route without treatment. Skin temperature was monitored every 10 min using electronic thermocouple probes (BTM-4208SD; Sato-Tech, Kanagawa, Japan), and was maintained at 18–20 °C or 40–42 °C for cooling and warming, respectively.

2.4. Macroscopic evaluation

Extravasation injury to skin was evaluated macroscopically according to a method described previously [18]. Briefly, the widest perpendicular diameters of skin lesions were measured using a caliper by an investigator blinded to group allocation. Each lesion site was inspected every day during the first week after intradermal injection, then every 5 days from day-7. Four parameters of lesions (erythema, induration, ulceration, necrosis) were assessed. The area of lesion sites was calculated in cm^2 as the product of diameters [18]. The area under the lesion–time curve (AUC) was calculated in cm^2 days using the trapezoidal method [18]. The AUC, peak area of the lesion, and damage duration were analyzed until the injury healed completely.

2.5. Histopathologic evaluation

Lesion sites were biopsied (using a dermal punch) with a diameter of 4 mm at 24 h after intradermal injection according to the peak time of lesions using phenytoin (which is thought to possess strong alkaline properties similar to those of thiopental) [20]. Tissue samples were suspended in 10% formaldehyde for fixation before dehydration, Sections (5 μm) from the paraffin-embedded tissue blocks were stained with hematoxylin and eosin, in addition to standard histopathologic evaluation under a light microscope (BX51; Olympus, Tokyo, Japan). Each sample was analyzed by independent pathologists blinded to the experimental procedure.

2.6. Statistical analyses

Data are the mean $\pm$ standard error of the mean (SEM). Differences among each treatment group were analyzed using Kruskal–Wallis test followed by the Student Newman–Keuls multiple-comparison *post hoc* test. $P < 0.05$ was considered significant.

3. Results

3.1. Macroscopic findings

For saline-injected rats, no change was observed at any injection site. In thiopental-treated rats, skin lesions developed immediately and reached maximal intensity within 24 h after injection (Fig. 1a). At 2–3 days after thiopental injection, the epidermis had regenerated and exhibited eschar formation, granulation and excoriation of necrotic sites. Typical shape of these skin lesions was ovoid, and induration, erythema, and ulceration (in descending order of size) were observed. Epidermal integrity was
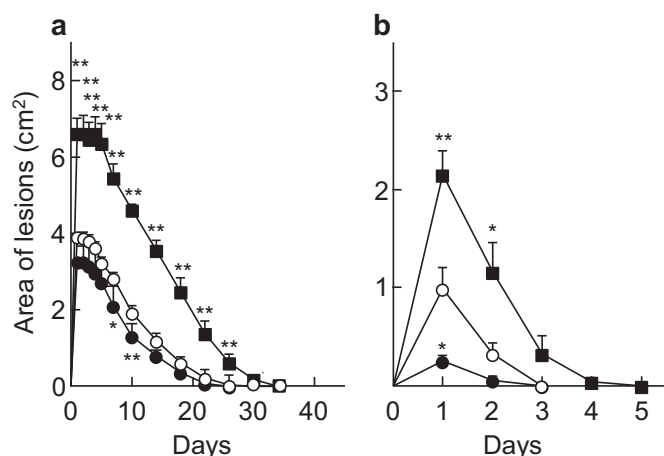
Fig. 1. Effects of local cooling or warming on macroscopic injury induced by thiopental (a) or propofol (b) extravasation in rats. Thiopental (2.5 mg) or propofol (1.0 mg) were administered intradermally (ID) at a volume of 100 μL. Local cooling (18–20 °C) and warming (40–42 °C) were performed for 3 h immediately after ID of thiopental or propofol. Remaining lesions were monitored until the injury was healed completely. Open circles, closed circles and closed squares represent lack of treatment, cooling and warming, respectively. Each value represents the mean ± SEM of results from five rats. $^*P < 0.05$, $^{**}P < 0.01$: significantly different from controls (non-treatment).

Table 1
Effects of local cooling or warming on thiopental- and propofol-induced skin lesion parameters in rats.

Agent/Treatment	Peak area (cm²)	AUC (cm² days)	Damage duration (days)
Thiopental			
None	3.9 ± 0.2	42.0 ± 2.3	20.9 ± 0.9
Cooling	3.3 ± 0.2	31.5 ± 2.1	17.6 ± 1.1*
Warming	6.6 ± 0.5**	98.4 ± 6.2**	26.8 ± 1.3**
Propofol			
None	1.0 ± 0.2	1.3 ± 0.3	1.5 ± 0.2
Cooling	0.3 ± 0.1*	0.3 ± 0.1	1.1 ± 0.2
Warming	2.2 ± 0.2**	3.7 ± 0.7**	2.2 ± 0.3

AUC, area under the lesion-time curve. Thiopental (2.5 mg) and propofol (1.0 mg) were administered intradermally (ID) at a volume of 100 μL. Local cooling (18–20 °C) and warming (40–42 °C) were performed for 3 h immediately after ID of thiopental or propofol. Remaining lesions were monitored until the injury was completely healed. Each value represents the mean ± SEM of results from five rats.

* $P < 0.05$.
** $P < 0.01$: significantly different from controls (non-treatment).

returned completely over 18–27 days. Local cooling slightly improved skin lesions as represented by the peak area of lesions, AUC, and damage duration ($p < 0.05$). Warming significantly increased the peak area and AUC by ≈ 1.7-fold ($p < 0.01$) and 2.3-fold ($p < 0.01$) compared with those in the control group, respectively (Table 1). Damage duration was also extended by ≈ 6 days in warming-treated rats compared with that in control rats ($p < 0.01$). Propofol injection also induced maximal skin lesions within 24 h (as shown in thiopental-treated rats). Lesions in propofol-treated rats had subtle erythema but no ulceration (unlike those in thiopental-treated rats). Propofol-induced lesions healed within 2 days compared with the 18–27 days needed by thiopental-treated rats (Fig. 1b and Table 1). Thus, the extent of propofol-induced lesions was much milder compared with that induced by thiopental. Local cooling reduced the peak area ($p < 0.05$), AUC and damage duration, whereas warming increased the peak area ($p < 0.01$), AUC ($p < 0.01$) and damage duration (Table 1).

3.2. Histopathologic findings

In saline-treated control rats, skin tissue showed cells with intact architecture as well as regular morphology of skin tissue (Fig. 2a, b). At 24 h after thiopental injection, degeneration, edema, necrosis and infiltration of inflammatory cells were observed in epidermal, dermal and subcutaneous tissues (Fig. 2c, d). In good agreement with macroscopic findings, local cooling suppressed the edema and degeneration in muscle seen in thiopental-treated rats, suggesting that cooling also reduced the skin disorders caused by thiopental injection at the morphologic level (Fig. 2e, f). In contrast, warming promoted more severe degeneration and necrosis in epidermal, dermal, subcutaneous tissues, blood-vessel walls and muscle compared with those in untreated rats (Fig. 2g, h). Some nuclear debris was observed in the deep dermis of these warmed rats. These results clearly suggested that skin lesions induced by thiopental injection in warmed rats was the most severe among the three groups. Propofol injection did not result in necrosis, but led to more inflammatory cells infiltrating into dermal and subcutaneous tissues and muscle in untreated controls compared with those in thiopental-treated rats. Furthermore, cooling and warming did not affect the lesions of propofol-injected rats at the histopathologic level (Fig. 3).

4. Discussion

Recognition of the potential risks for extravasation of agents is very important. However, the risks of extravasation injury induced by thiopental and propofol are understood incompletely because extravasation injuries caused by these agents has not been evaluated at macroscopic and histopathologic levels. We examined the intrinsic risks of extravasation injury by thiopental and propofol and classified them into three categories according to macroscopic and histopathologic findings of skin damage using a rat model. Effects of local cooling or warming of tissue on extravasation injury were also evaluated.

Thiopental injection induced skin lesions such as erythema, induration, ulceration and tissue necrosis within 24 h after its extravasation (Fig. 1a). In good agreement with macroscopic findings, histopathologic evaluation of skin lesions showed degeneration, edema, and necrosis in the epidermal, dermal and subcutaneous tissues of thiopental-treated rats within 24 h (Fig. 2). These results suggest that extravasation injury due to thiopental is severe, and we classified thiopental as a "vesicant". With respect to the mechanism of tissue damage from extravasation of non-cytotoxic agents, the high osmolarity, acidic or alkaline pH and/or vasoconstrictive activity have been reported [3]. According to manufacturer instructions, thiopental injection leads to an osmotic pressure ratio of 0.8 and alkaline pH of 10.2–11.2. Thus, the ulceration and necrosis induced by thiopental could be attributed to its alkalinity rather than its osmolarity. Propofol caused an inflammatory reaction with erythema, but ulceration was not observed macroscopically in the extravasation site. Histopathologic evaluation showed that propofol exerted no vesicant effects (including induction of necrosis though the increased number of inflammatory cells infiltrating into the dermis and subcutaneous tissue) (Fig. 3). Thus, we categorized propofol as an "irritant", in agreement with previous reports [8–11]. Propofol has been recognized as a less invasive drug because of its chemical properties, isotonicity, and neutral pH (7.0–8.5) [8]. However, even a less invasive agent such as propofol can induce tissue injury if large volumes of solution are extravasated because high hydrostatic pressures lead to tissue ischemia [21,22]. Propofol can leak readily because it is injected forcefully using automated syringe drivers. Thus, tissue compression by large volumes of extravasated
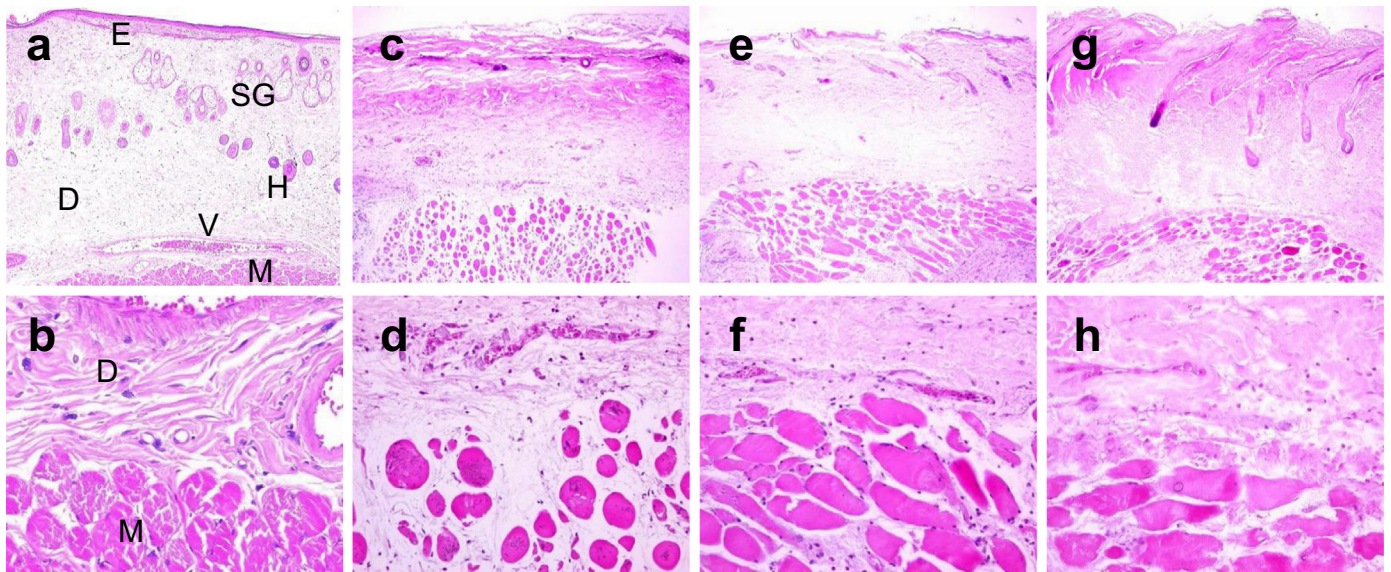
Fig. 2. Effects of local cooling or warming on histopathological skin lesions induced by thiopental extravasation in rats. Normal skin (a, b) after intradermal injection (ID) of saline shows complete architectural construction of dermis, skin appendixes, epithelium (E), dermis (D), muscle (M), hair follicle (H), sebaceous glands (SG), vessel (V). Control (c, d) is a group without any treatment after ID of thiopental (2.5 mg). Cooling treated with cold pack (18–20 °C) for 3 h immediately after thiopental ID, reduced edema (e, f). Warming treated with hot pack (40–42 °C) for 3 h immediately after thiopental ID, caused degeneration and necrosis in the deep dermis and muscle (g, h). Hematoxylin and eosin stain: (a, c, e, g) magnification × 4; (b, d, f, h) magnification × 20.
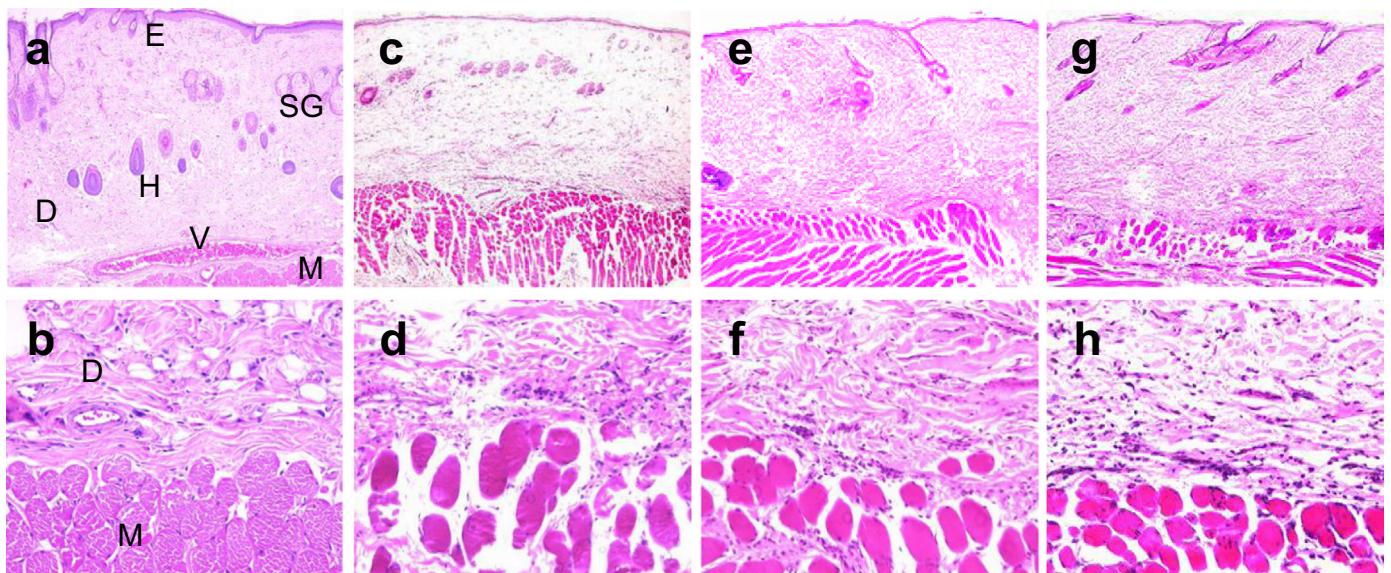

Fig. 3. Effects of local cooling or warming on histopathological skin lesions induced by propofol extravasation in rats. Normal skin (a, b) after intradermal injection (ID) of saline shows complete architectural construction of dermis, skin appendixes, epithelium (E), dermis (D), muscle (M), hair follicle (H), sebaceous glands (SG), vessel (V). Control (c, d) is a group without any treatment after ID of propofol (1.0 mg). Cooling (e, f) treated with cold pack (18–20 °C) for 3 h immediately after propofol ID and warming (g, h) treated with hot pack (40–42 °C) for 3 h immediately after propofol ID. Skin tissues were biopsied at 24 h after ID of saline or propofol. Hematoxylin and eosin stain: (a, c, e, g) magnification × 4; (b, d, f, h) magnification × 20.

solution may be involved in the development of skin toxicity by extravasated propofol. In addition, several reports have shown that skin necrosis by propofol is involved in malnutrition and predisposition to the bleeding caused by sepsis and diabetes mellitus [12,23,24]. Thus, further study is needed to confirm that propofol is an irritant by distinguishing the intrinsic risk properties of agents and other risk factors (e.g., physical destruction of tissue due to excess accumulation of injected fluid in connective tissues).

With regard to the management of extravasation injury induced by cytotoxic agents, application of cooling or warming and pharmacologic agents (e.g., dexrazoxane for anthracycline and hyaluronidase) has been reported [25]. We examined the effects of cooling or warming on extravasation injury induced by thiopental and propofol because these supportive measures are conservative. Cooling reduced the severity of thiopental-induced lesions, including edema and necrosis in dermal, subcutaneous and intramuscular tissue. The mechanism of injury reduction by cooling may be due to the induction of vasoconstriction, which results in reduced dispersion of these agents [25]. Dorr et al. reported that warming can reduce the extravasation injury caused by vinca alkaloids though mechanisms that are understood incompletely [26]. In contrast, in our study, warming exacerbated rather than improved the extravasation injury caused by thiopental at macroscopic and histopathologic levels. Warming also exacerbated the severity of macroscopic skin lesions in propofol-treated rats, but exerted no histopathologic changes in propofol-treated rats

(Fig. 3). The reason for this difference in the effect of warming on propofol-induced injury at macroscopic and histopathologic levels is not clear. Dispersion of these agents away from the extravasation site, and promotion of an inflammatory reaction and/or edema resulting from the increased blood circulation by warming, could be considered as mechanisms of exacerbation [1,3,15]. Conversely, local warming in combination with an acidic agent (e.g., lidocaine) could improve the extravasation injury induced by alkaline agents because warming enhances the neutralization of alkaline agents by lidocaine resulting from promotion of their dispersion [3].

Studies have shown that dimethyl sulfoxide (DMSO) improves anthracycline-induced tissue injuries by scavenging free radicals [27,28]. Extravasation of alkaline agents, as well as anthracycline agents, generates free radicals such as the hydroxide radical [29]. Hence, topical administration of DMSO could enable scavenging of the free radicals generated by extravasated alkaline agents. DMSO also promotes redistribution of poorly water-soluble extravasated agents from lesions into the systemic blood circulation by increasing their solubility [25]. Thiopental and propofol are poorly soluble in water but have high solubility in DMSO. Thus, a combination of topical DMSO and cooling applied after extravasation could improve the skin lesions induced by these agents by scavenging free radicals and/or promoting removal of these agents from tissues to a greater extent compared with cooling alone.

Systematic methods of cooling and warming, such as the compression time and temperature for extravasation injury, have not been determined [22]. Multiple cooling or warming poultices have been applied to reduce extravasation injury (e.g., four-times daily for 20-min each for 1–2 days) [29]. Protection, rest, ice, compression, and elevation have been used for ankle-joint sprains [30] and muscle bruises, as has cryotherapy [31]. Thus, multiple cooling may be effective for treatment of the skin lesions induced by thiopental and propofol. Oyama et al. reported that a single 3-h cooling session caused a greater reduction in counts of inflammatory cells expressing C5a receptor 1 and interleukin-8 receptor, and a peripheral nerve fiber bundle expressing transient receptor potential vanilloid type 1 than four-times daily cooling for 20 min in doxorubicin-injected mice [32], suggesting that using a poultice for 20 min may not be sufficient to treat the extravasation injury cause by vesicants. However, so far, there are no data demonstrating whether multiple cooling or single cooling is more relevant to treat skin lesions induced by extravasated thiopental and propofol. In our study, single cooling at 18–20 °C for 3 h reduced the inflammation and ulceration caused by thiopental and propofol. Thus, we recommended use of a cool poultice for the 3 h to treat the extravasation injury by thiopental or propofol. Warm compresses must be avoided to treat the extravasation injury caused by these agents. This information could provide a reference for identification of the risk of extravasation of propofol or thiopental, and management of such extravasation.

Appendix A. Transparency document

Transparency document associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.bbrep.2016.09.005.

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