Clinical Study

Efficacy and Safety of Halometasone Cream to Treat Chronic Generalized Eczema and the Effects of Halometasone Cream on Serum Cortisol Levels

Yan Li, Wei Xu, and Linfeng Li

Department of Dermatology, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China

Correspondence should be addressed to Wei Xu; 2403649155@qq.com

Received 19 August 2017; Accepted 19 October 2017; Published 9 November 2017

Copyright © 2017 Yan Li et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The aim of the study was to investigate the efficacy and safety of halometasone cream to treat chronic generalized eczema and the effects of halometasone cream on serum cortisol (COR) levels. Sixty consecutive outpatients diagnosed with chronic generalized eczema between January and April 2017 were included and divided into groups A, B, and C with a lesion area of 30%–40%, 41%–50%, and 51%–60%, respectively. Groups A, B, and C were treated with halometasone cream with a daily dose of 15 g, 20 g, and 30 g for 7–14 days, respectively. Ten patients were randomly selected from each group for serum COR measurement at days 0, 7, and 14. On day 14, group B had significantly higher cure rate (47.1%) than groups A (17.9%) and C (13.3%) and significantly higher effectiveness rate (82.4%) than group C (40.0%) (all $P < 0.05$). Serum COR levels were not affected in group A but were reduced significantly in groups B and C on days 7 and 14 (all $P < 0.05$). No adverse reaction was observed. Halometasone cream appeared to relieve chronic generalized eczema effectively and safely. High dosage ($\geq 20$ g daily for 14 days) may temporarily reduce endogenous COR production substantially, although it may be more effective.

1. Introduction

Eczema is a skin inflammatory disease and can be caused by multiple intrinsic and extrinsic factors. Chronic generalized eczema, a common type of eczema, is characterized by lesions occurring at multiple sites, complex etiology, persistent recurrence, and severe pruritus. The disease substantially reduces the quality of life of patients and imposes serious economic burden on patients [1]. Topical glucocorticoid (GC), which is commonly used to treat eczema in clinical practice, can usually relieve eczema-associated symptoms such as inflammation and pruritus rapidly [2]. Topical GC use at a proper dosage is quite safe and barely causes adverse reactions [3]. However, patients with chronic generalized eczema often use topical GC for a long time and at a relatively high dose. Wester and colleagues have found that long-term use of topical GC may cause GC to enter circulation system through skin absorption, resulting in reversible hypothalamic-pituitary-adrenal axis suppression and the consequent systemic adverse reactions [4]. Courreau and colleagues have demonstrated that the weekly dose of topical propionic acid chloride betamethasone cream should be less than 50 g in order to prevent GC-associated severe adverse reactions [5].

Halometasone cream is a commonly used high-potency topical GC. It inhibits inflammation, epidermal hyperplasia, and allergic reactions, constrict blood vessels, and relieve pruritus. The mechanism of action of halometasone is that the drug can bind to steroid receptors to modulate the protein synthesis that is involved in the development of chronic generalized eczema and thus to regulate the function of inflammatory cells and lysosomes and ultimately to reduce inflammatory responses [6–8]. According to the instruction of halometasone cream, only 1.41% of halometasone cream used for consecutive 7 days on a lesion area of 400 cm$^2$ can be absorbed via the skin. However, the dosage of halometasone cream use in the real world is often higher than the recommended dosage provided by the manufacturer. The effects of topical halometasone cream on serum cortisol (COR) levels remain unknown.

The current study aims to evaluate the efficacy and safety of halometasone cream to treat chronic generalized eczema
and examine the effects of halometasone cream on serum COR levels. This study also provides clinical evidence for an effective and safe dosage of halometasone cream to treat the disease.

2. Materials and Methods

2.1. Study Design. This prospective cohort study included consecutive outpatients visiting the Department of Dermatology of Beijing Friendship Hospital for chronic generalized eczema from January to April 2017. The study protocol has been approved by the Institutional Review Board of Beijing Friendship Hospital (Approval number 2017-P2-010-02). All of the participating patients signed the informed consent form.

2.2. Patient Inclusion and Exclusion Criteria. The patient inclusion criteria were as follows: (1) a confirmed diagnosis of chronic generalized eczema according to the diagnostic criteria [10]; (2) the disease severity being at least moderate (Investigator's Global Assessment Score ≥ 3); (3) the skin lesions being at multiple sites and affected 30% to 60% of the total body surface area; (4) the target lesions being at the limbs or trunk and showing a diameter of 2 cm to 10 cm; (5) adult patients aged 18 to 80 years; (6) voluntarily signing the informed consent form.

The exclusion criteria were as follows: (1) skin lesions accompanied with infection of viruses, bacteria, and/or fungi; (2) the eczema on the face and skin-folding areas; (3) systemic use of glucocorticoid and/or immunosuppressant and/or ultraviolet light therapy within 4 weeks before the enrollment interview; (4) local use of glucocorticoid and/or oral use of antihistamines within two weeks before the enrollment interview; (5) severe disease in the liver, kidney, and/or blood; (6) autoimmune diseases, chronic serious infection, diabetes, mental diseases, substance abuse, and/or alcoholic; (7) the malignant tumor or other serious diseases that may compromise the accuracy of efficacy evaluation for the study drug; (8) any other condition that the investigators believed could interfere in the study; (9) pregnant, breastfeeding, or planning to become pregnant during the study period; (10) being allergic to the study drugs; (11) failing to follow the study protocol.

2.3. Intervention. Patients received the topical treatment of halometasone cream (trade name Aoneng, Hongkong Bright Future Pharmaceutical, Ltd., batch number: 1601508) twice daily. After the cream was applied, the treated area was massaged for 5 minutes until the cream was absorbed completely. For patients with a lesion area of 30%–40% (Group A), 41%–50% (Group B), and 51%–60% (Group C), the daily dose of the halometasone cream was 15g, 20g, and 30g, respectively. The treatment course was 7 days. Patients were followed up every 7 days and the efficacy of the halometasone cream was evaluated. The treatment was ended on day 7 when the skin lesions were cured; otherwise, the treatment was continued for another 7 days. Adverse events were recorded during each follow-up examination. Clinical observation was ended on day 14 for all of the participating patients.

2.4. Serum Cortisol (COR) Measurement. Ten patients were randomly selected from each group for serum cortisol (COR) measurement on days 0, 7, and 14. Three mL venous blood was withdrawn at 8 a.m. before breakfast on days 0, 7, and 14. Patients with abnormal serum COR after the treatment with halometasone cream were required to come back for serum COR measurement 28 days after the termination of the treatment (day 42 in total). Serum COR levels were determined using the UniCel DxI 800 chemiluminescence immunoassay system (Beckman Coulter, USA) following the manufacturer’s instruction. All reagents were provided by the manufacturer (Beckman Coulter, USA). The normal range of serum COR levels was 6.0–23.0 μg/dL.

2.5. Halometasone Cream Efficacy Assessment. At the enrollment interview and each follow-up examination, the severity, shape, and area of skin lesions were determined. The shape of skin lesions was defined as erythema (E), induration/papulation (I), excoriation (Ex), and lichenification (L). The severity score was 0, 1, 2, or 3 representing none, light, moderate, or severe, respectively. Lesion area score was 0, 1, 2, 3, 4, 5, or 6 representing that 0%, <10%, 10%–29%, 30%–49%, 50%–69%, 70%–89%, or 90%–100% of the each body region area were affected by the skin lesions, respectively. Eczema area and severity index (EASI) was calculated according to the following equation: head/neck lesion area score × total head/neck severity score (E + I + Ex + L) × 0.1 + upper limb lesion area score × total upper limb lesion severity score (E + I + Ex + L) × 0.2 + trunk lesion area score × total trunk lesion severity score (E + I + Ex + L) × 0.3 + lower limb lesion area score × total lower limb lesion severity score (E + I + Ex + L) × 0.4 [9]; efficacy index = (EASI before treatment − EASI after treatment) ÷ EASI before treatment × 100%. Completely effective, significantly effective, effective, and not effective were defined as an efficacy index > 90%, 60%–89%, 20%–59%, and <20%, respectively. Effectiveness rate = the number of cases showing completely effective + the number of cases showing significantly effective) ÷ total number of cases × 100% [11].

2.6. Halometasone Cream Safety Assessment. Adverse reactions to halometasone cream were monitored during the study. Adverse reactions were discovered by telephone interviews and in-person follow-up examinations. The severity of adverse reactions was graded as mild, moderate, and severe. Treatments and outcomes of adverse reactions were recorded.

2.7. Statistical Analyses. The statistical analysis software SPSS 16.0 was used to analyze data. Numerical data are presented as mean ± standard deviation (SD). Intragroup comparison was analyzed by paired t-test and repeated measures ANOVA. Categorical data are presented as rate and compared by Chi-square test. P value was two-sided, and P < 0.05 was considered statistically significant.

3. Results

3.1. Patient Baseline Characteristics. A total of 60 patients (37 men and 23 women) with chronic generalized eczema were
Table 1: Baseline characteristics.

|                       | Total  | Group A  | Group B  | Group C  | P value |
|-----------------------|--------|----------|----------|----------|---------|
|                       | N = 60 | N = 28   | N = 17   | N = 15   |         |
| Age (year)            |        |          |          |          |         |
| Range (Min, Max)      | 22–78  | 23–78    | 32–74    | 22–78    |         |
| Mean ± SD             | 54.7 ± 16.1 | 54.8 ± 14.8 | 55.0 ± 14.0 | 54.1 ± 21.0 | 0.985   |
| Sex                   |        |          |          |          |         |
| Men, n (%)            | 37 (61.7) | 15 (53.6) | 15 (88.2) | 7 (46.7) | 0.026* |
| Women, n (%)          | 23 (38.3) | 13 (46.4) | 2 (11.8) | 8 (53.3) |         |
| Lesion area (%)       | 30–60  | 30–40    | 41–50    | 51–60    |         |
| Disease history (month) |        |          |          |          |         |
| Range (Min, Max)      | 2–240  | 3–240    | 6–120    | 2–240    |         |
| Mean ± SD             | 61.5 ± 57.6 | 55.8 ± 46.5 | 53.8 ± 33.7 | 80.7 ± 89.4 | 0.332   |
| Lesion status         |        |          |          |          |         |
| EASI, Mean ± SD       | 30.7 ± 8.7 | 23.9 ± 4.2 | 34.0 ± 7.5 | 39.8 ± 4.9 | <0.0001* |
| Serum COR, Mean ± SD (µg/dL) | 10.9 ± 3.1 | 11.1 ± 4.3 | 10.9 ± 2.7 | 10.7 ± 2.0 | 0.967   |

SD: Standard deviation. EASI: eczema area and severity index. COR: Cortisol. One-way ANOVA was performed to compare the three groups. *P < 0.05 was considered significant different. 1Significantly higher versus group B (P = 0.004) and group A (P < 0.0001). 2Significantly higher versus group A (P < 0.0001).

Patients were enrolled (N = 60)

Group A (n = 28)
Lesion area: of 30%–40%
Daily dose: 15 g/d

Group B (n = 17)
Lesion area: of 41%–50%
Daily dose: 20 g/d

Group C (n = 15)
Lesion area: of 51%–60%
Daily dose: 30 g/d

Group A
(i) Treated (n = 28)
(ii) Efficacy and adverse event assessment (n = 28)

Group B
(i) Treated (n = 17)
(ii) Efficacy and adverse event assessment (n = 17)

Group C
(i) Treated (n = 15)
(ii) Efficacy and adverse event assessment (n = 15)

Figure 1: Patient flowchart.

Patients were screened (N = 105)

Excluded in total (N = 45)
(i) Failed to meet the inclusion criteria (N = 23)
(ii) Refused to sign the informed consent (N = 9)
(iii) Refused to come back for follow-up examine (N = 13)

enrolled in the study. Patient flowchart is shown in Figure 1. Patients’ baseline characteristics are displayed in Table 1. The 60 patients had a broad range of age (22–78 years), disease course (2–240 months), and skin lesion area (30%–60%). According to the skin lesion area, the 60 patients were divided into three groups: group A (n = 28) with a lesion area of 30%–40%, group B (n = 17) with a lesion area of 41%–50%, and group C (n = 15) with a lesion area of 51%–60%. Notably, the proportion of men and EASI were significantly different in the three groups (P < 0.05, Table 1). The mean EASI of group C (39.8 ± 4.9) was the highest in the three groups (Table 1) and significantly higher than that of group B (34.0 ± 7.5, P = 0.004) and of group A (23.9 ± 4.2, P < 0.0001). Group B had significantly higher average EASI than
Halometasone cream is a potent topical GC drug and widely used in clinical practice. In the current study, the dosages
Table 3: Halometasone cream efficacy.

|                  | Total | Group A | Group B | Group C | P value |
|------------------|-------|---------|---------|---------|---------|
|                  | N = 60| N = 28  | N = 17  | N = 15  |         |
| Follow-up visit at day 7 |       |         |         |         |         |
| Complete effective, N (%) | 5 (8.3) | 2 (7.1) | 2 (11.8) | 1 (6.7) |         |
| Significant effective, N (%) | 16 (26.7) | 8 (28.6) | 5 (29.4) | 3 (20.0) |         |
| Effective, N (%) | 26 (43.3) | 14 (50.0) | 6 (35.3) | 6 (40.0) |         |
| No effect, N (%) | 13 (21.7) | 4 (14.3) | 4 (23.5) | 5 (33.3) |         |
| Cure rate¹ (%) | 8.3 | 7.1 | 11.8 | 6.7 | 0.832 |
| Effectiveness rate² (%) | 35.0 | 35.7 | 41.2 | 26.7 | 0.688 |

Follow-up visit at day 14

|                  | Total | Group A | Group B | Group C | P value |
|------------------|-------|---------|---------|---------|---------|
|                  | N = 60| N = 28  | N = 17  | N = 15  |         |
| Complete effective, N (%) | 15 (25.0) | 5 (17.9) | 8 (47.1) | 2 (13.3) |         |
| Significant effective, N (%) | 23 (38.3) | 13 (46.4) | 6 (35.3) | 4 (26.7) |         |
| Effective, N (%) | 14 (23.3) | 7 (25.0) | 2 (11.8) | 5 (33.3) |         |
| No effect, N (%) | 8 (13.3) | 3 (10.7) | 1 (5.9) | 4 (26.7) |         |
| Cure rate¹ (%) | 25.0 | 17.9 | 47.1¹ | 13.3 | 0.044* |
| Effectiveness rate² (%) | 63.3 | 64.3 | 82.4² | 40.0 | 0.046* |

¹Cure rate = the number of cases showing complete effective ÷ total number of cases. ²Effectiveness rate = (the number of cases showing complete effective + the number of cases showing significant effective) ÷ total number of cases × 100% [9]. Chi-square test was used to compare the difference of the three groups. *P < 0.05 was considered significant different. ¹Significantly higher versus group A (P = 0.036) and group C (P = 0.04). ²Significantly higher versus group C (P = 0.014).

Figure 3: Representative photos of lesions before and after treatment of a patient from group B. (a) Lesion on day 0, EASI = 21.6. (b) Lesion on day 7, EASI = 9.6, efficacy index = 55.6%. (c) Lesion on day 14, EASI = 8.1, efficacy index = 62.5%.

of halometasone cream for the three patient groups were determined based on the previous report by Long and Finlay [12]. In their report, to guide dermatologists to prescribe a precise dosage of topical GC, the authors firstly proposed fingertip unit (FTU) [12]. A FTU is defined as the amount of topical GC cream that is from a standard 5 mm diameter topical medication tube and is enough to cover the area of the index finger from the fingertip to the nearest index finger joint [12]. One FTU is approximately equivalent to 0.5 g. The area of one hand accounts for approximately 1% of the total body surface area. One FTU (0.5 g) is for 2% of the total body surface area. Thus, one FTU per time for twice daily is equal to 1 g daily. The topical GC dosage used to treat bullous pemphigoid has been calculated according to lesion area and severity, and daily dose of topical propionic acid chloride betamethasone cream for mild, moderate, and severe bullous pemphigoid is 20 g, 30 g, and 40 g, respectively [13, 14]. Based on these previous reports [12–14], we determined the daily dosages for the three patient groups as 15 g for a lesion area of 30%–40%, 20 g for 41%–50%, and 30 g for 51%–60% in the current study.

This study found that the cure rate and effectiveness rate of one-week halometasone cream treatment for chronic generalized eczema were 8.3% and 35.0%, respectively, and the rates were increased to 25.0% and 63.3% as the treatment duration was increased to 2 weeks. Thus, halometasone cream alone appears to treat chronic generalized eczema rapidly and effectively. Previous studies have shown similar results [8, 15]. On day 14 of the treatment, group B showed significantly higher cure rate than the other two groups, suggesting that a daily dose of 20 g may be the optimal dose for patients with a lesion area of 41%–50%. Possible reasons for the lowest cure rate and effectiveness rate of group C may be associated with the relatively longer disease history
In the current study, the treatment did not affect serum extent of topical GC-associated serum COR reduction [17, dose and medication duration of topical GC may affect the endogenous COR production. Thus, long-term topical use of hypothalamus and anterior pituitary to downregulate increases serum COR levels, which triggers negative feedback with the baseline value. Topical use of GC can transiently significantly reduced serum COR levels after 7 and 14 days for patients with severe chronic generalized eczema. halometasone cream for two weeks, which could downregulate the GC receptors on epidermal keratinocytes and microvascular endothelial cells and consequently compromise the efficacy and anti-inflammatory effects of the topical GC [16]. Furthermore, the efficacy index of group C was not increased at day 14 compared with that at day 7, suggesting that daily 30 g of halometasone cream for two weeks may not be very effective for patients with severe chronic generalized eczema.

The serum COR levels of group A were not affected by the treatment. However, patients in the groups B and C showed significantly reduced serum COR levels after 7 and 14 days of the treatment. Serum COR levels in group C on day 14 of the treatment were even lower than the normal COR levels. In particular, after 14 days of treatment, the serum COR levels of group C were reduced by 85.6% compared with the baseline value. Topical use of GC can transiently increase serum COR levels, which triggers negative feedback to hypothalamus and anterior pituitary to downregulate endogenous COR production. Thus, long-term topical use of GC may actually reduce endogenous COR production. The dose and medication duration of topical GC may affect the extent of topical GC-associated serum COR reduction [17, 18]. In the current study, the treatment did not affect serum COR in group A, indicating that topical use of daily 15 g of halometasone cream for 14 days may not affect endogenous COR production in patients with a lesion area of 30%–40%.

In contrast to the low dosage of halometasone cream, daily dose ≥ 20 g appeared to reduce endogenous COR production substantially. In particular, daily 30 g for only 7 days resulted in 71.0% decrease in serum COR levels. The high-dose halometasone cream-associated serum COR reduction was temporary. Serum COR levels were restored to normal levels 28 days after the termination of the treatment.

There are limitations in the current study. The sample size is relatively small. Only 10 patients in each group were measured for serum COR levels. Thus, the findings of the current study need to be verified by larger scale studies.

5. Conclusions

Topical use of low-dose halometasone cream alone appeared to relieve the symptoms of chronic generalized eczema effectively, rapidly, and safely. Daily 15 g for 14 days did not affect endogenous COR production. Although daily dose of 20 g for 14 days showed 82.4% effectiveness rate in patients with a lesion area of 41%–50%, serum COR levels of the patients were significantly reduced. Daily dose of 30 g for 7 days temporarily reduced serum COR to levels lower than the normal levels. Thus, we recommend avoiding high-dose halometasone cream to treat chronic generalized eczema.

Conflicts of Interest

The authors have not disclosed any potential conflicts of interest.

Acknowledgments

This study was supported by a research grant from China Society of Integrated Traditional Chinese and Western Medicine-Skin Disease Research Fund.

References

[1] Q. Li, Y. Yang, R. Chen et al., “Ambient air pollution, meteorological factors and outpatient visits for eczema in Shanghai, China: A time-series analysis,” International Journal of Environmental Research and Public Health, vol. 13, no. 11, article no. 1106, 2016.
[2] R. Maiti, C. S. Sirka, N. Shaju, and D. Hota, “Halometasone monohydrate (0.05%) in occupational contact dermatitis,” Indian Journal of Pharmacology, vol. 48, no. 2, pp. 128–133, 2016.

[3] A. Das and S. Panda, “Use of topical corticosteroids in dermatology: an evidence-based approach,” Indian Journal of Dermatology, vol. 62, no. 3, pp. 237–250, 2017.

[4] V. L. Wester, G. Noppe, M. Savas, E. L. T. van den Akker, Y. B. de Rijke, and E. F. C. van Rossum, “Hair analysis reveals subtle HPA axis suppression associated with use of local corticosteroids: The Lifelines cohort study,” Psychoneuroendocrinology, vol. 80, pp. 1–6, 2017.

[5] B. Coureau, J.-F. Bussières, and S. Tremblay, “Cushing’s syndrome induced by misuse of moderate- to high-potency topical corticosteroids,” Annals of Pharmacotherapy, vol. 42, no. 12, pp. 1903–1907, 2008.

[6] D. V. S. Pratap, M. Philip, N. T. Rao et al., “Evaluation of efficacy, safety, and tolerability of fixed dose combination (FDC) of halometasone 0.05% and fusidic acid 2% w/w topical cream versus FDC of betamethasone valerate 0.12% and neomycin sulphate 0.5% w/w topical cream in the treatment of infected eczematous dermatosis in Indian subjects: A randomized open-label comparative phase III multi-centric trial,” Indian Journal of Dermatology, vol. 58, no. 2, pp. 117–123, 2013.

[7] N. Goswami, V. R. M. Gupta, and H. A. Jogia, “Development and validation of a novel stability-indicating RP-HPLC method for the simultaneous determination of halometasone, fusidic acid, methylparaben, and propylparaben in topical pharmaceutical formulation,” Scientia Pharmaceutica, vol. 81, no. 2, pp. 505–518, 2013.

[8] The Excare Working Group, “Halometasone 0.05% cream in eczematous dermatoses,” Journal of Clinical and Aesthetic Dermatology, vol. 6, no. 11, pp. 39–44, 2013.

[9] J. M. Hanifin, M. Thurston, M. Omoto, R. Cherill, S. J. Tofte, and M. Graeber, “The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis,” Experimental Dermatology, vol. 10, no. 1, pp. 11–18, 2001.

[10] J. I. Silverberg and A. S. Paller, “Association between eczema and stature in 9 US population-based studies,” JAMA Dermatology, vol. 151, no. 4, pp. 401–409, 2015.

[11] Y.-P. Bai, D.-Q. Yang, and Y.-M. Wang, “Clinical study on treatment of acute eczema by Shuangfujin,” Zhongguo Zhong Xi Yi He Za Zhi Zhongguo Zhongxiyi Jiehe Zazhi, vol. 27, no. 1, pp. 72–75, 2007.

[12] C. C. Long and A. Y. Finlay, “The finger-tip unit—a new practical measure,” Clinical and Experimental Dermatology, vol. 16, no. 6, pp. 444–447, 1991.

[13] J. B. Terra, W. J. B. Potze, and M. F. Jonkman, “Whole body application of a potent topical corticosteroid for bullous pemphigoid,” Journal of the European Academy of Dermatology and Venereology, vol. 28, no. 6, pp. 712–718, 2014.

[14] P. Joly, J.-C. Roujeau, J. Benichou et al., “A comparison of two regimens of topical corticosteroids in the treatment of patients with bullous pemphigoid: A multicenter randomized study,” Journal of Investigative Dermatology, vol. 129, no. 7, pp. 1681–1687, 2009.

[15] H. R. Jerajani, A. S. Kumar, M. Kuruvila et al., “Efficacy and safety of topical halometasone in eczematous dermatoses in Indian population: An open label, noncomparative study,” Indian Journal of Dermatology, vol. 56, no. 6, pp. 652–656, 2011.

[16] A. Billich, H. Aschauer, A. Aszödi, and A. Stuetz, “Percutaneous absorption of drugs used in atopic eczema: pimecrolimus permeates less through skin than corticosteroids and tacrolimus,” International Journal of Pharmaceutics, vol. 269, no. 1, pp. 29–35, 2004.

[17] B. Sahu, M. Laakso, P. Pihlajamaa et al., “FoxA1 specifies unique androgen and glucocorticoid receptor binding events in prostate cancer cells,” Cancer Research, vol. 73, no. 5, pp. 1570–1580, 2013.

[18] S. Cialfi, R. Palermo, S. Manca et al., “Glucocorticoid sensitivity of T-cell lymphoblastic leukemia/lymphoma is associated with glucocorticoid receptor-mediated inhibition of Notch1 expression,” Leukemia, vol. 27, no. 2, pp. 485–488, 2013.