Hong Kong J. Dermatol. Venereol. (2016) **24**, 120-128

Review Article

Effectiveness of external topical medications in the treatment of keloid scars: a review

文獻回顧：外部外用藥物在瘢痕瘤的治療成效

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Keloid scars may cause itch, pain and psychological distress. Topical medications are easily administered, painless, and accessible. This article reviews their effectiveness. The primary and secondary outcomes were scar size and symptom reduction respectively. Ten randomised controlled trials were included, involving 317 subjects. Four papers showed topical silicone reduced keloid size, two reported no improvement. Addition of vitamin E was superior to silicone gel sheeting alone in reducing scar symptoms. Onion extract and hydration and occlusion showed a reduction in scar size and symptoms. Most evidence supports the use of silicone. Further trials are needed to evaluate alternative external medications.

瘢痕瘤疤痕可以構成瘙癢、疼痛和心理困擾。外用藥物不單使用方便和無痛，且容易獲取。本文回顧了瘢痕瘤外部外用藥物的功效。首要和第二成果分別被設定爲疤痕的大小和症狀減少。我們篩選了十個隨機對照試驗，共涉及 317 名患者。當中有四個研究顯示外用矽膠減少了瘢痕瘤的大小，反之兩個報告沒有改善。而添加了維生素E的矽凝膠膜對改善疤痕症狀的效果，優勝於單獨使用。洋葱提取物和水潤及密封亦顯示出能減少疤痕的大小和症狀。總括來說，大多數證據都支持矽膠的使用，而其他的替代外部藥物，側需進一步研究評估。

Keywords: External, keloid, scar, topical, treatment

關鍵詞：外部、瘢痕瘤、疤痕、外用、治療

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Introduction

Keloids are elevated fibrous scars that result from a derailment in the normal wound-healing process and can grow over many years. Keloids occur more commonly amongst people of coloured skin than of white skin.[1] Skin injury in adolescents and young adults is more likely to lead to scarring and keloid formation than for a similar injury in an elderly person.[2] Recent data on ambulatory keloid management in the United States found that the

mean age of patients seeking treatment was 36.6 years.[3]

Keloids, especially those longstanding (>10 years) and on non-visible areas of the body, are more likely to cause physical symptoms such as itch, pain, and movement restriction.[3] Keloid symptoms also correlate positively with psychological issues such as poor satisfaction with appearance, shame of disease, and suffering.[4]

Being able to initiate effective first-line treatment for keloids will limit the utilisation of healthcare resources, value-add to the practice, and boost confidence in the long-term doctor-patient relationship. Treatment options for keloid scars range widely from external topical medications, to intra-lesional injections, radiation therapy, cryotherapy, laser therapy, and surgical excision. All of these modalities have demonstrated favourable treatment outcomes with comparable results.[5]

External topical medications are simple to administer, painless, and easily accessible. Patients are more amenable to external topical treatments, compared to more aggressive therapies, which can also be more painful and costly. To date, there has been no comprehensive evaluation of the data on the relative efficacies of the various external topical preparations in keloid management.

This article is an overview of the current external topical treatments for keloid scars, and evaluates the various therapies.

Materials and Methods

Studies were identified through an electronic search of PubMed (through-January 2014) and the Cochrane library databases - Cochrane Central Register of Controlled Trials (no restrictions) and Cochrane Database Systematic Reviews (no restrictions). Articles containing the following Mesh terms were included: keloid, scar, treatment, therapy, and therapeutics. This was further supplemented by reviewing bibliographies from the relevant articles.

Studies were included if they were (1) a randomised controlled trial (2) involved treatment of patients with established keloids (3) evaluated an external topical keloid treatment, and (4) written in the English language. Articles were excluded if (1) treatment was for hypertrophic scars alone, if (2) treatment was for fresh surgical wounds alone, or if (3) the treatment process involved surgical keloid excision.

The two authors assessed the relevance of each retrieved study independently, and decided whether it should be included in the analysis. Divergences were resolved by consensus. The analysis in this article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

Through the electronic database search, 131 abstracts were identified. By review of abstracts, 11 papers were selected for full text analysis. Fifteen further studies were found from the review of bibliographies of the relevant articles. Amongst these, a total of 10 studies fulfilled all the selection criteria and were included in the final analysis. The progress of the study selection is summarised in Figure 1.

Each chosen study was classified according to the following features (Scar type, participant numbers, intervention, outcome measures, follow-up, drop-out rate, results). The overall methodological quality of each randomised controlled trial was appraised according to the Jadad scale.[6] Scoring took into account the methods of randomisation and blinding, and assessed for a description of withdrawals and dropouts. Scoring ranged from 0 to 5 points, with a higher score corresponding to a more rigorous trial.

The primary outcome studied was reduction in scar size. The secondary outcomes evaluated were symptoms pertaining to the keloid, including pain, and itch. The studies included were reported descriptively with continuous data presented as mean and standard deviation, and categorical data as frequency and percentage. P values where available were reported with a $p<0.05$ taken to be significant. The heterogeneity of the selected trials (different treatment, different outcome measures, difference in data reported) precluded the combined analysis of outcomes with the exception of two papers (Tan et al[7] and Gold[8]). This analysis was carried out using RevMan 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and a fixed-effect method was used to obtain risk ratios (RR) with 95% confidence intervals (CI) for the combined outcomes.

Results

All 10 included trials compared a topical treatment with either a control or another treatment. In total, there were 317 subjects aged 2-81 years. The studies spanned six countries, comprising of Asia[7,16] (2 studies), USA[8,10,11,14,15] (5 studies), Europe,[12,13] (2 studies), and South America (1 study).[9] All were single-centre trials with follow-up duration ranging from 2-5 months.

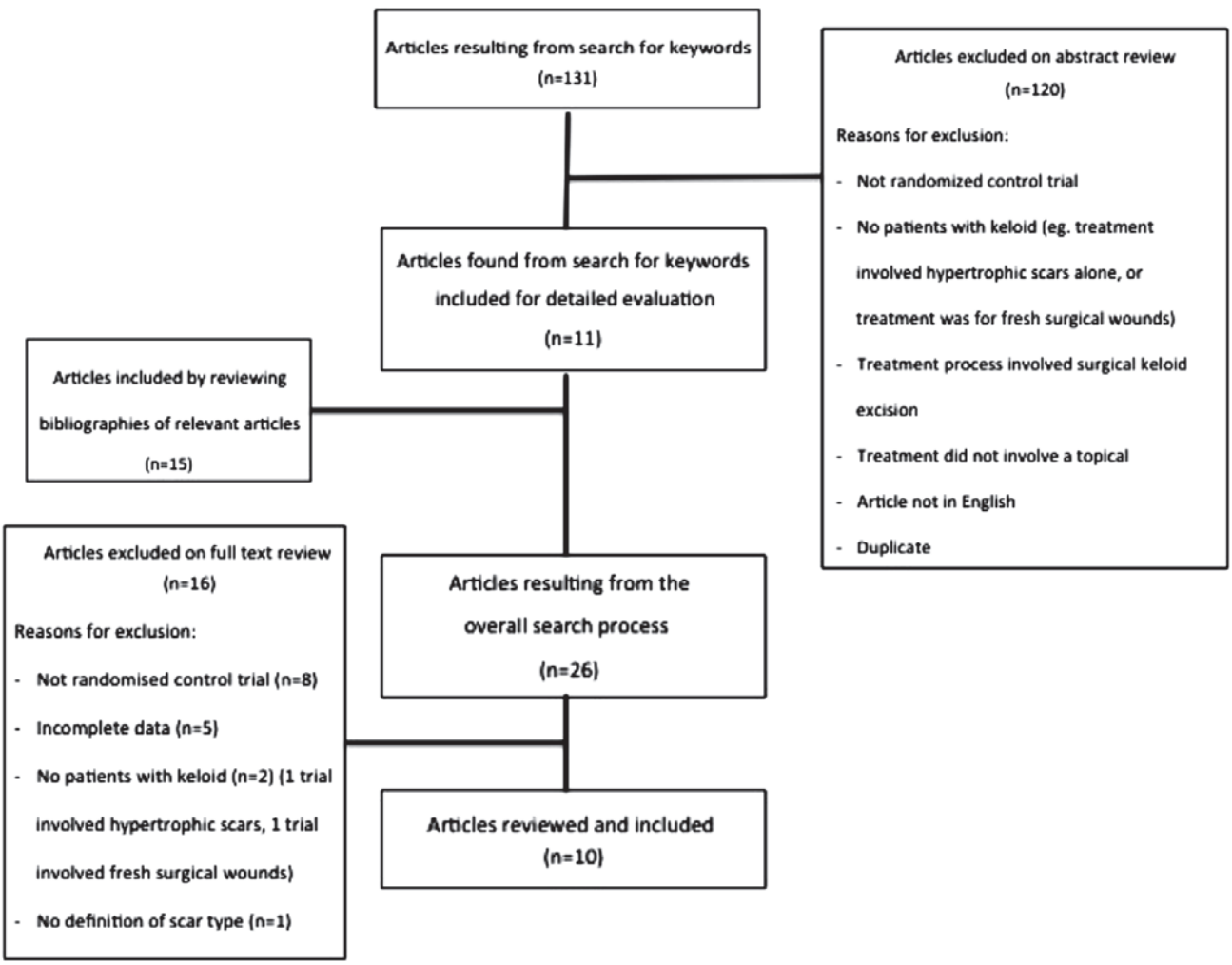

Figure 1. The process of the study selection.

Nine trials studied patients with hypertrophic scars and keloids.[8-16] Amongst them, three studies reported the results for keloid scars separately.[8,9,15] One Asian paper focused solely on keloids.[7] Six studies evaluated the use of topical silicone (in either the gel or sheet form).[7-12] One trial studied the use of a combination lotion containing 0.5% hydrocortisone, silicone and vitamin E (HSE).[14] Two papers investigated the use of onion extract gel (OE).[13-14] Three other trials studied non-silicone gel,[9] hydrocolloid dressing,[15] and hydration with occlusion[16] respectively.

Amongst the trials, there was variation in the objective parameters used to determine the primary outcome of scar size reduction. These included scar elevation, length, width, and scar volume. Secondary outcome measures were also evaluated using several different measurement techniques and tools. This made pooling of the results difficult. The characteristics of each included study are summarised in Tables 1 to 4.

Table 1. Silicone gel/gel sheet versus no treatment

Author	Scars studied	Participant no. (keloids/ total)	Interventions		Outcome measures		Follow -up	Drop-outs n(%)	Results	Jadad score
			Intervention (n=keloids/ total)	Control (n=keloids/ total)	Objective	Subjective				
Tan, 1999[7]	K ≥2yr	20 pt with 40 K/20	S sheet (n=20/20)	No treatment (n=20/20)	Size, Photograph	Pain, Itch, Colour, Texture	12wk	3 (15)	- 12% in S arm achieved ≥50% scar size reduction (p>0.05)	1
†Gold, 1994[8]	K and HS, split scar study	4/21	S sheet (n=4/21)	No treatment (n=4/21)	Thickness, Photograph	Colour	12wk	0	- 3 K had 'some improvement'; 1 K had no change (p value *).	2
†De Oliveira, 2001[9]	K and HS ≥3mth	8 pt with 25 K/26 pt with 41 scars	S sheet (n=8/16 scars)	No treatment (n=10/11 scars)	Length, Width, Intra-cicatricial pressure	Pain, Itch, Colour, Induration	135d	0	- Reduced scar length and width in S arms (p=0.001). - Reduced intracicatricial pressure in S arms (p=0.045). - Improved scar colour (p=0.001), and induration (p<0.0001) in S arm. - No significant difference in pain or itch in treatment arm vs controls.	2
Chernoff, 2007[10]	K, HS, and healing scars	*/30 pt with 60 scars	S gel (n=*/10) S sheet (n=*/10) S gel day, S sheet night (n=*/10)	No treatment (n=*/30)	Elevation, Photograph, Punch biopsy	Erythema, Softening, Itch, Irritation, Skin maceration	90d	0	- Reduced scar elevation in gel and gel sheet treatment arms vs controls (p<0.001). Greater reduction in scar elevation with gel vs gel sheet. - Reduced erythema (p<0.001), itch, irritation or skin maceration (p≤0.001) in gel and gel sheet arms vs controls.	1

K=keloids; HS=hypertrophic scars; S=silicone; Pt=patient, vs=versus; yr=year; mth=month; wk=week; d=day

*not reported; †keloid outcomes analysed separately

Table 2. Comparison of the different types of external silicone preparations

Author	Scars studied	Participant no. (keloids/ total)	Interventions		Outcome measures		Follow -up	Drop-outs n(%)	Results	Jadad score
			Intervention (n=keloids/ total)	Control (n=keloids/ total)	Objective	Subjective				
Berman, 1999[11]	K and HS ≥7mth	22/32	S gel-filled cushion (n=*/16)	S gel sheet (n=*/16)	Length, Width, Volume	Tenderness, Itch, Colour, Induration, Patient satisfaction	16wk	9 (28)	- 53% volume reduction with gel-filled cushion vs 36.3% with gel sheet (sig change from baseline, no significant difference between treatment arms). - Equal reduction in tenderness, itch, and degree of softening between treatment arms.	2
Palmieri, 1995[12]	K and HS, ≥3mth	*/80	Vit E added S gel sheet (n=*/40)	S gel sheet (n=*/40)	Photograph	Pain, Itch	8wk	0	- Results for scar size not reported - 95% in Vit E arm vs 75% in non-Vit E arm achieved >50% symptom improvement ($p<0.05$).	3

K=keloids; HS=hypertrophic scars; S=silicone; Vit=vitamin; vs=versus; yr=year; mth=month; wk=week
*not reported

Table 3. Use of topical onion extract

Author	Scars studied	Participant no. (keloids/ total)	Interventions		Outcome measures		Follow -up	Drop-outs n(%)	Results	Jadad score
			Intervention (n=keloids/ total)	Control (n=keloids/ total)	Objective	Subjective				
Koc, 2008[13]	K and HS ≥1yr	18/27	iTAC wkly x 4, and OE (n=9/14)	iTAC wkly x 4 (n=9/13)	Elevation, Photograph	Pain, Itch, Erythema, Induration	20wk	0	- 95.9% reduction in scar elevation in OE arm vs 68.1% in iTAC alone arm ($p<0.05$). - Greater reduction in pain and itch in the onion extract arm (p value *).	2
Perez, 2010[14]	K and HS	8 in final analysis /20	OE (n=4 in final analysis/10)	Placebo moisturising lotion (n=4 in final analysis/10)	Volume, Photograph	Cosmesis, Pain, Itch, Erythema, Pigmentation, Induration	16wk	10(50)	- OE ($p=0.01$) and placebo ($p=0.02$) both reduced scar volume from baseline. No significant difference between groups. - OE improved cosmetic appearance ($p<0.01$), tenderness ($p<0.05$), pigmentation ($p<0.001$), and induration ($p<0.01$) over placebo.	4

K=keloids; HS=hypertrophic scars; S=silicone; iTAC=intralesional triamcinolone acetonide; OE=onion extract gel; Pt=patient, vs=versus; yr=year; wk=week; wkly= wkly=weekly
*not reported

Table 4. Other non-silicone external topicals versus no treatment/moisteuriser

Author	Scars studied	Participant no. (keloids/ total)	Interventions		Outcome measures		Follow -up	Drop-outs n(%)	Results	Jadad score
			Intervention (n=keloids/ total)	Control (n=keloids/ total)	Objective	Subjective				
Perez, 2010[14]	K and HS	7 in final analysis/20	HSE (n=3 in final analysis/10)	Placebo moisturising lotion (n=4 in final analysis/10)	Volume, Photograph	Cosmesis, Pain, Itch, Erythema, Pigmentation, Induration	16wk	10 (50)	- HSE (p=0.01), and placebo (p=0.02) both reduced scar volume from baseline. No significant difference between groups. - HSE improved cosmetic appearance (p<0.01), erythema (p=0.01), pigmentation (p<0.001), and induration (p<0.001) over placebo.	4
†De Oliveira, 2001[9]	K and HS, ≥3mth	8 pt with 25 K/26 pt with 41 scars	Non-S gel sheet (n=7/ 14 scars)	No treatment (n=10/ 11 scars)	Length, Width, Intra-cicatricial pressure	Pain, Itch, Colour, Induration	135d	0	- Reduced scar length and width in non-S arm (p=0.001). - Reduced intra-cicatricial pressure in non-S arms (p=0.045). - Improved scar colour (p=0.001), and induration (p<0.0001) in treatment arm vs controls. - No significant difference in pain or itch in treatment arm vs controls.	2
†Phillips, 1996[15]	K and HS	2/20	Hydrocolloid dressin (n=1/10)	Moisturising cream (n=1/10)	Elevation, Transcutaneous oxygen, Photograph	Pain, Itch, Erythema, Pigmentation, Pliability, Oedema, Vascularity	8wk	*	- No change outcome measures for K.	2
Sawada, 1992[16]	K and HS. Split scar study	4/31	B-cream with impermeable plastic film (n=4/31)	Vaseline (n=4/31)	Elevation	Pain, Itch, Erythema, Hardness	20wk	0	- Reduction in elevation, pain, itch, erythema, and hardness in B-cream arm vs controls (p<0.05).	1

K=keloids; HS=hypertrophic scars; S=silicone; HSE=0.5% Hydrocortisone, Silicone, and Vitamin E lotion; B-cream=stearic acid, cetanol, liquid paraffin, lanolin, tri-ethanol, glycerin, water; Pt=patient, vs=versus; mth=month; wk=week

*not reported; †keloid outcomes analysed separately

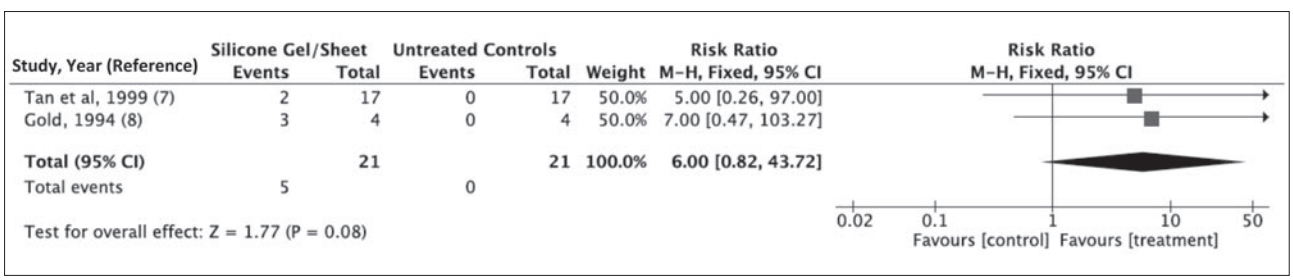

Figure 2. Meta-analysis of risk ratios from studies of silicone gel/sheet.

Primary outcome

Topical silicone (in the form of gel or gel sheeting) was found in three trials to reduce keloid size when compared to non-treatment.[8-10] However, one study showed that topical silicone gel was no better than untreated controls.[7] A combined analysis of outcomes from two of these papers (Tan et al,[7] and Gold[8]) showed an overall trend towards improvement (Figure 2), although this was not statistically significant (RR 6; 95%CI 0.82-43.72).

HSE was equivalent to placebo.[14] Another trial reported silicone gel and non-silicone gel to be equally effective.[9] Silicone gel was found to be inferior to intralesional triamcinolone acetonide (iTAC) in one paper.[7]

The relative efficacy of the various types of topical silicone was evaluated in two papers,[11,12] of which neither showed any difference. The gel sheet and gel-filled cushion had equal effect.[11] There was a trend towards decreased scar height with silicone gel as compared to silicone gel sheeting, but this was not statistically significant.[10] OE as used alone is no better than placebo.[14] However when used in combination with iTAC, OE produced better reductions in scar elevation.[13] Hydrocolloid dressing showed no benefit over moisturising cream,[15] while hydration and occlusion treatment was superior to simple Vaseline.[16] Non-silicone gel was better than placebo.[9]

Secondary outcomes

One study reported reduction in scar-associated symptoms with topical silicone (in the form of gel and gel sheeting) compared with untreated controls.[10] HSE was better than placebo.[14] One paper found silicone gel sheet no better than untreated controls in reducing pain or itch, but effective in reducing scar color and induration.[9]

Silicone gel-filled cushion was as effective as the gel sheet in producing symptomatic improvement.[11] However, silicone gel sheets added with vitamin E was superior to simple silicone gel sheets.[12] One trial found non-silicone gel sheeting as effective as silicone gel sheeting in reducing scar color and induration.[9]

OE improved keloid symptoms when used as a stand-alone,[14] or in combination with iTAC.[13] Hydration and occlusion was effective in reducing scar symptoms.[16]

Discussion

To our knowledge, this is the first comprehensive review on the external topical treatments available for keloid scars. A recent review on post-sternotomy keloids focused mainly on non-topical as well as intra-lesional therapies.[17] These included surgery, laser treatment, intra-lesional triamcinolone and intra-lesional 5-fluorouracil.

Amongst the various external topical treatments, the use of topical silicone to treat keloid disease is the best-studied. The precise mechanism of action of silicone is unknown; but silicone is believed to function in a manner analogous to the stratum corneum, acting as an impermeable membrane to promote cutaneous hydration.[18]

The appeal of topical silicone lies in its ready availability, ease of use, and good safety profile. Silicone gel is more convenient to administer compared with gel sheeting, which has to be worn for 10-24 hours daily. Our review has demonstrated topical silicone to be effective in reducing the size and symptoms of keloids. However, evidence regarding the most superior preparation of topical silicone is inconclusive.

Data is lacking on the relative efficacy of topical silicone compared with other treatment modalities. There was only one study here comparing topical silicone gel to iTAC, but the sample size was small.[7] A meta-analysis of 70 treatment series for keloids and hypertrophic scars did not show any statistically significant differences between

treatment outcomes of the various therapeutic modalities.[5] However, this study did not analyze the outcomes for keloids and hypertrophic scars separately. In addition, the paper did not include any trials that directly compared external topical therapy with a non-topical treatment modality.

From our review, OE has shown promising initial results in the treatment of established keloids. To date however, the number of randomised controlled clinical trials done in this aspect is limited. The use of OE has also been evaluated in the area of scar prevention, with conflicting results.[19-21]

Imiquimod 5% cream and corticosteroid ointment has been tested as adjuvants to surgical excision. A pilot study using imiquimod cream after shave-excision did not reduce keloid recurrence rate.[22] A case series combining corticosteroid injection and ointment application after keloid excision demonstrated reduced recurrence rate.[23] No trials have been done to assess imiquimod or external corticosteroid preparations alone as a first-line treatment modality.

The effectiveness of alternative external topical remedies such as mugwort lotion, *Centella asiatica* extract, topical vitamin E, adhesive taping, and massage therapy have not been borne out in randomised controlled trials.

There are several limitations noted. Firstly, several trials included a mixture of subjects with keloids and hypertrophic scars. These two entities differ in their natural histories and treatment responses. Hypertrophic scars remain confined to the original wound site and regress with time, whilst keloids have the potential to grow beyond the margins of injury and proliferate indefinitely.[24,25] Secondly, the majority of the trials had small sample sizes and assessed only short-term outcomes. The long-term efficacy of topical keloid treatment remains to be further evaluated. Thirdly, there were subtle differences in the primary outcomes of the two trials chosen for combined analysis, although this was unlikely to make a difference to the overall treatment effect. Finally, several trials were not blinded and this may introduce bias, especially when assessing secondary outcomes, which may be subjective.

Conclusion

This review highlights that different external topical treatments have shown varying efficacies for the treatment of keloids. Most evidence exists for the use of topical silicone in the reduction of keloid size. More rigorously designed randomised controlled trials with larger sample sizes and longer durations of follow-up are needed to evaluate the other external topical treatments. Keloid therapy combining different treatment modalities is another promising area of research.

Acknowledgements

No funding was received for this study. All names authors meet the ICMJE criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

Conflict of interest

Both authors declare that they have no conflict of interest.

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