Does silicone gel migrate via lymphatics after subcutaneous injection?

Philip P Narini MD, John L Semple MD MSc FRCSC, John B Hay PhD, Stan J Lugowski MSc,

Dennis Smith MSc, PhD, DSc, FRCS

Departments of Pathology and Immunology, Sunnybrook Health Science Centre, Division of Plastic Surgery, Women's College Hospital, Centre for Biomaterials, University of Toronto, Toronto, Ontario

PP Narini, JL Semple, JB Hay, SJ Lugowski, D Smith. Does silicone gel migrate via lymphatics after subcutaneous injection? Can J Plast Surg 1994;2(2):67-70. Reports have documented the presence of elemental silicon, evidence of silicone elastomer, or silicone polymers (gel) in lymph nodes and other sites distant from implanted prostheses. It has been suggested that this occurs via the lymphatic system; however, the mechanism of spread or migration of silicone has not been previously studied. This study investigated the possible role of lymphatics in the migration of silicone gel. In the sheep model, it is possible to obtain continuous samples of both afferent and efferent lymph by cannulating lymphatic vessels. The drainage areas of subcutaneous lymph nodes in the sheep have previously been studied. In our model, the efferent lymphatic vessel from the prefemoral lymph node was cannulated to obtain samples of lymph (efferent and 'pseudoafferent'). After baseline samples were collected, 3 to 5 mL of free silicone gel was injected subcutaneously in the drainage area of this node. Samples (5 to 10 mL) of lymph were continuously collected (for up to 50 days), sealed, stored at -20°C, and then submitted as a group for trace element analysis to quantitate the levels of elemental silicon. No statistically significant increase was seen in baseline levels of elemental silicon after silicone gel injections. Statistically significant higher levels of silicon were found in afferent (mean 799 ± 22 part per billion [ppb]) compared with efferent lymph (mean 607 ± 19 ppb). This experimental study did not identify significant increases in elemental silicon levels in lymphatic vessels after the subcutaneous introduction of free silicone gel. Higher levels were found in afferent versus efferent lymph. This implies that migration of silicone gel does not occur soon after the exposure of a subcutaneous space to free silicone gel, or that the migration of silicone gel may occur by a cellular mechanism that can bypass the lymphatic vessels.

Key Words: *Lymph, Lymphatics, Migration, Sheep, Silicone gel*

Le gel de silicone migre-t-il par le système lymphatique après injection sous-cutanée?

RÉSUMÉ : Certains rapports notent la présence de silicone élémentaire, d'élastomère de silicone ou de polymère de silicone (gel) dans les ganglions lymphatiques et dans d'autres endroits éloignés des prothèses implantées. Il a été suggéré que ces particules suivent le réseau lymphatique. Toutefois, le mécanisme de propagation ou de migration du silicone n'avait encore jamais été étudié. Cette étude s'est penchée sur le rôle possible du réseau lymphatique dans la migration du gel de silicone. Dans un modèle de mouton, il est possible d'obtenir des échantillons continus, tant dans la lymphe afférente que efférente, par la canulation des vaisseaux lymphatiques. Les zones de drainage des ganglions lymphatiques sous-cutanés avaient déjà été étudiées chez le mouton. Dans notre modèle, le vaisseau lymphatique efférent à partir du ganglion lymphatique préféromal a été canulé afin d'obtenir des échantillons de lymphe (efférente et «pseudo-efférente»). Après la cueillette des échantillons de départ, 3 à 5 mL de gel de silicone libre ont été injectés par voie sous-cutanée dans la zone de drainage de ce ganglion. Des échantillons de lymphe (5 à 10 mL) ont été recueillis (pendant un maximum de 50 jours), scellés et conservés à -20°C, puis soumis en groupe à une analyse des éléments traces, afin de quantifier les taux de silicone élémentaire. Aucune augmentation statistiquement significative n'a été observée par rapport au taux de silicone élémentaire de départ après les injections de gel de silicone. Des taux significativement plus élevés de silicone ont été découverts dans le réseau afférent (moyenne 799 ± 22 parties par milliard [ppm]) en comparaison avec la lymphe efférente (moyenne 607 ± 19 ppm). Cette étude expérimentale n'a pas identifié d'augmentation significative des taux de silicone élémentaire dans les vaisseaux lymphatiques après introduction sous-cutanée de gel de silicone libre. Des taux plus élevés ont été notés dans la lymphe afférente par rapport à la lymphe efférente. Cela suppose que la migration du gel de silicone ne survient pas peu de temps après l'exposition de l'espace sous-cutané du gel de silicone libre ou que la migration du gel de silicone peut se produire par l'entremise d'un mécanisme cellulaire qui outrepassse les vaisseaux lymphatiques.

One of the desirable properties of silicone gel as a component of soft-tissue implants is its cohesiveness. It was initially felt that even with rupture of a silicone gel-filled implant, this cohesive property, coupled with the recognized formation of a fibrous capsule surrounding the implant, would prevent silicone gel from 'migrating' to distant sites

(1). However, silicone lymphadenopathy has been well reported following rupture of silicone-gel filled implants (2-5). Also, the presence of various forms of silicones in sites distant to the initial site of implantation has been documented (6-11).

It is speculated that this migration of silicone may occur via a blood or lymph vascular route (12,13). There is evidence that increased levels of silicone may occur in blood (6,9,14). There is no direct experimental or clinical evidence to support the hypothesis that silicones may travel via lymph through a lymphatic vessel.

The aim of this study is to investigate the trace levels of

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Correspondence and reprints: Dr JL Semple, Division of Plastic Surgery, University of Toronto, Women's College Hospital, Burton Hall, 60 Grosvenor Street, Second Floor, Toronto, Ontario. M5S 1B6. Telephone (416) 323-6115, Fax (416) 921-4275

elemental silicon in lymph, before and after the introduction of subcutaneous silicone gel. A sheep model is used which allows the collection of both afferent and efferent lymph and in which the drainage areas of various subcutaneous lymph compartments has been previously documented.

MATERIALS AND METHODS

Animals

Four randomly bred ewes (between the ages of eight and 12 months) were kept in metabolism cages and allowed free access to food and water. Two of the animals had prefemoral nodectomies performed at least one month previously. This allows for the spontaneous anastomosis of the tiny afferent vessels with the large and easily accessible efferent lymphatic. Hence, cannulation of the efferent prefemoral lymphatic allows for the collection of afferent lymph. These animals will be referred to as A1 and A2. Similarly, the other two animals (E1 and E2) had an efferent lymphatic vessel cannulated for the collection of efferent lymph.

Collection of lymph

The efferent lymphatic vessel of the prefemoral subcutaneous lymph node was cannulated as previously described (15,16). Briefly, after anaesthetic induction by intravenous injection of thiopental sodium, anaesthesia was maintained via endotracheal intubation with halothane (Halocarbon Laboratories, North Augusta, USA). The efferent lymphatic from the prefemoral lymph node was identified on the reflected surface of the quadriceps muscle and cannulated using a 0.96 mm clear vinyl catheter (Dural Plastics and Engineering, Auburn, Australia). Lymph was continuously collected in a heparinized-penicillin solution in a sterile bottle sutured to the skin.

Free silicone gel (3 to 5 mL) was injected subcutaneously, using a large bore needle, in the area drained by the prefemoral lymph node of the sheep. The silicone gel had been removed, under meticulous sterile conditions, from a silicone gel filled implant (style 80 Gel Filled/Round Mammary Implant, McGhan Medical Corp, Santa Barbara, USA). Evan's blue dye was also injected to provide a colorimetric method to confirm that the injection took place in an area drained by the node (ie, the lymph turns blue after injection). Samples of lymph were collected at regular intervals before and after injection of silicone gel. The experiment was terminated when the catheter was pulled out by the animal or it clotted and flow could not be re-established.

Contamination precautions

One of the difficulties with such a study is the ease by which elemental silicon can be introduced as a contaminant due to its ubiquitous nature. Strict precautions were followed throughout the experiment.

Bottles were prepared to ensure no trace element contamination. They were rinsed with n-heptane, soaked for 24 h in detergent and rinsed five times with distilled water. They were then washed with trace metal grade concentrated hydrochloric acid and allowed to soak for a few hours; the solution

Figure 1 Trace level of silicon in afferent lymph. No specific pattern of level of silicon is demonstrated in the afferent lymph of two sheep. Silicone gel was injected subcutaneously at time $t=0$ h

Figure 2 Trace level of silicon in efferent lymph. No specific pattern of level of silicon is demonstrated in the efferent lymph of two sheep. Silicone gel was injected subcutaneously at time $t=0$ h

was then diluted and allowed to stand overnight, then rinsed five times with distilled water and twice with deionized water, dried in an oven at 60° C, and then stored in a polyethylene bag.

Samples (5 to 10 mL) of lymph (plasma and cells) were collected directly into these prepared bottles, sealed with Parafilm, and stored at -20° C in a polyethylene bag until the termination of each experiment. They were then taken to the Centre for Biomaterials, University of Toronto, for determi-

Figure 3) Mean trace levels of silicon in lymph. No statistically significant increased level of silicon is demonstrated after injection of silicone gel in four sheep. Mean values ($\pm$ SEM) for afferent lymph sampled from sheep A1 and A2 are: pre injection 882 ± 38 ppb, post injection 752 ± 27 ppb. Values in efferent lymph sampled from sheep E1 and E2 are: pre injection 582 ± 28 ppb, post injection 613 ± 22 ppb. A statistically significant higher mean level of silicon was identified in afferent lymph (799 ± 22 ppb) compared with efferent lymph (607 ± 19 ppb)

nation of trace levels of elemental silicon. Any handling of samples was done with polyethylene gloves.

Determination of silicon

All sample preparation was done under Class 100 laboratory conditions. Elemental silicon was measured using graphite furnace atomic absorption spectrophotometry (Varian Model 875 with graphite furnace Model GTA 95 and autosampler). Calibration curves were performed using standard solutions containing 750 mg/L silicon progressively diluted in lymph plasma.

No standard reference materials are available for silicon levels in tissues or for polydimethylsiloxane. Hence, results were reported as levels of elemental silicon in ng/g or parts per billion (ppb).

Statistical analysis

Data were presented graphically and expressed as ppb. Although it may be more appropriate to express the data in histogram or scatter diagram form, it was felt that, for clarity, a line graph was appropriate. Since each experiment was sufficiently different from the others (afferent versus efferent, different collection times) the data were not pooled.

An analysis of variance was performed on the raw data which identified no statistically significant differences between levels of silicon in efferent lymph. In afferent lymph, there was no statistically significant increase in silicon.

Comparison of afferent and efferent lymph did identify a statistically significant higher level of silicon in afferent lymph ($P < 0.0001$). A Student-Newman-Keuls test was performed with an $\alpha = 0.01$ to determine where the significant differences occurred.

RESULTS

Figure 1 shows the trace levels of silicon in afferent lymph collected from two sheep (A1 and A2) for the duration of each experiment. Figures 2 shows the trace levels of silicon in efferent lymph collected from two sheep (E1 and E2). No patterns of increased levels were demonstrated.

Figure 3 shows the mean levels of silicon ($\pm$ standard deviation) before and after injection of silicone gel in the drainage area of the sampled lymphatic vessel in four sheep. Pre and post injection levels of elemental silicon in ppb ($\pm$ SEM) were: Afferent lymph pre 882 ± 38 ppb, post 752 ± 27 ppb; Efferent lymph pre 582 ± 28 ppb, post 613 ± 22 ppb. None of the animals demonstrated a statistically significant increased level post injection.

A statistically significant higher level of silicon was identified in afferent lymph (A1 757 ± 28 ppb, A2 862 ± 34 ppb, mean 799 ± 22 ppb) compared with efferent lymph (E1 606 ± 26 ppb, E2 608 ± 27 ppb, mean 607 ± 19 ppb) (Figure 3), with no statistically significant difference between animals in each group.

DISCUSSION

Silicone lymphadenopathy has been described with various forms of implanted silicones (2-5,7-9,17). It has been demonstrated that inflammatory cells can phagocytose silicones and that silicone can induce foreign body giant cell granulomas locally and at sites distant from the implanted silicone (6,18,19,20). Local spread of injected silicone liquid has been reported (21). Also, rupture of silicone gel filled implants, either spontaneous or as a result of external capsulotomy (22,23), can lead to local migration of silicone with granuloma formation (24,25) or problems such as transcutaneous extravasation of silicone gel (26) or constrictive neuropathy (27). Intuitively, silicones could migrate to local or distant sites via the lymphatic system, and this mechanism has been proposed (12,13).

The goal of this study was to measure the trace level amounts of elemental silicon in the lymph drained from a subcutaneous area which has previously had silicone gel injected. Both afferent and efferent lymph were examined as one may postulate the lymph node as acting as a 'filter' and preventing the passage of foreign material. Examination of both afferent and efferent lymph did not detect increased levels of elemental silicon after silicone gel injection. The levels detected do correspond with those recently measured by direct current atomic emission spectroscopy in human tissues (28).

Interestingly, higher levels were found in afferent lymph when compared with efferent lymph. This may be due to the presence of a different population of cells (ie, 15% of cells are macrophages) in afferent lymph (efferent lymph contains essentially pure lymphocytes). The significance of this finding is not known.

This study, which relied on continuous collection of lymph, is limited by the short-term nature, with the longest collection being 50 days. The amount of silicone injected may be considered too small an amount to be detected. However, it was felt that this amount would closely represent a clinical situation in which a silicone containing implant bled small amounts of silicone subcutaneously or in which small amounts of silicones are used for soft-tissue augmentation. The detection limit of the assay used is approximately 6 ppb. If one assumes that 3 mL of silicone gel are injected and that this is composed of polydimethylsiloxane (PDMS) (since the constituents of silicone gel are not available), then 1.13 g of elemental silicon were injected (PDMS is 37.8% elemental silicon). In the worst case, one could assume that all the silicone left the site of injection and equilibrated throughout all the tissues of a 30 kg sheep. This would result in a concentration of $1.13\text{g}/30\text{ kg} = 3.7 \times 10^4\text{ ng/g}$ (or ppb). That is, the concentration of elemental silicon would increase by a

factor of 10,000. Therefore, if only a very small percentage of the injected gel migrated via lymph, it would have been detected by our methods. Nevertheless, it remains possible that, over prolonged periods of time, silicone gel does reach the lymph nodes via afferent lymph. In the future, technical improvements should permit comparable measurements being made on solid tissues like lymph nodes.

SUMMARY

This study measured trace levels of elemental silicon in lymph from experimental animals having had an injection of unaltered silicone gel subcutaneously. No increased level of silicon was identified in the lymph after observation up to 50 days. Variations in silicon levels were found between afferent and efferent lymph. The significance of this is not known. This study does not support the hypothesis that silicon can migrate via the lymph, in sheep, after injection of unaltered free silicone gel.

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