Protective Covering of Surgical Wounds With Honey Impedes Tumor Implantation

Ismail Hamzoğlu, MD; Kaya Sarıbeyoğlu, MD; Haydar Durak, MD; Tayfun Karahasanoğlu, MD; İbrahim Bayrak; Tuncay Altuğ, MD; Feridun Sirin, MD; Muzaffer Sarıyar, MD

Hypothesis: Tumor implantation (TI) development at the surgical wound following cancer surgery is still an unresolved concern. Trocar site recurrence, which is likely a form of TI, has become one of the most controversial topics and, with the widespread acceptance of laparoscopic surgery, has caused renewed interest in questions about TI. Honey has positive effects on wound healing. Physiological and chemical properties of honey might prevent TI when applied locally.

Design, Interventions, and Main Outcome Measures: Sixty BALB/c strain mice, divided into 2 groups, were wounded in the posterior neck area. Group 1 mice formed the control group, and group 2 mice had wounds coated with honey before and after tumor inoculation. All wounds were inoculated with transplantable Ehrlich ascites tumor. The presence of TI was confirmed in the wounded area by histopathological examination on the 10th day.

Results: Tumor implantation was achieved in all group 1 animals and verified by palpable mass and histopathological examination. In group 2 mice, although TI could not be detected macroscopically, it was revealed by pathological examination in 8 cases. Tumor implantation was less likely in group 2 mice (8 of 30 vs 30 of 30; \( P < .001 \)).

Conclusions: Tumor implantation was markedly decreased by the application of honey pre- and postoperatively. It is possible that the physiological and chemical properties of honey protected wounds against TI. Honey could be used as a wound barrier against TI during pneumoperitoneum in laparoscopic oncological surgery and in other fields of oncological surgery.

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TUMOR IMPLANTATION (TI) is a complex phenomenon still under study. Mechanisms and preventive measures are subject to investigation. After the first report1 concerning trocar site recurrence (TSR), there was concern about the increased incidence of TI associated with laparoscopic oncological surgery. Although numerous experimental studies2-8 showed an increased incidence of TSR, clinical trials9-11 did not confirm this finding. In any case, reports of TSR diminished the widespread use of laparoscopy in malignant disease and evoked the concern of TI once more.

Honey has long been used to accelerate wound healing.12-14 Physiological properties of honey such as hypertonicity, low pH, and hygroscopicity were thought to augment the healing process. Antibacterial effects were also attributed to these elements. Moreover, tumoricidal effects are associated with chemical compounds such as caffeic acid esters, which are present in honey.15,16

We hypothesized that the protective covering of wounds with honey may provide protection against TI by forming a tender film barrier, which could inhibit the attachment of tumor cells to the wound. In this study, a reproducible wound model was designed by creating an air sac in the posterior nuchal area of BALB/c mice to investigate the role of a honey barrier against tumor cell invasion.

RESULTS

A palpable mass (Figure 1), ranging from 0.5 to 3 cm (mean, 1.1 cm) in diameter, was detected in all group 1 mice and was confirmed as TI by histopathological examination (Figure 2). In group 2 mice, no palpable masses were detected but ulcers 0.3 cm in diameter were observed in 3 mice. Histopathological examination of group 2 mice revealed TI in 8 animals. Tumor implantation was verified by histopathological examination in 2 animals with ulcers, whereas examination revealed TI in 6 animals without any macroscopic abnormalities (Figure 3). Application of honey induced inflammatory cell infiltration to the wound cavity while preventing tumor cell invasion (Figure 4 and Figure 5). Tumor implantation was less likely in group 2 mice (8 of 30 vs 30 of 30; \( P < .001 \); \( \chi^2 = 34.7 \)).
Statistical analysis revealed that a protective covering of wounds with honey significantly reduced TI ($P < .001$).

**COMMENT**

Liotta and colleagues$^{17,18}$ proposed a 3-step hypothesis describing the sequence of biochemical events during tumor cell invasion of the extracellular matrix: attachment of the tumor cell, local proteolysis of the basal membrane, and locomotion of the tumor cells within the tissue. A wound barrier that has no deleterious effect on healing may protect the wound against tumor cell invasion by eliminating tumor cell attachment. Results of this study suggest that honey provides a simple, effective, and harmless barrier to TI. Furthermore, honey might inhibit the local proteolysis step by altering the wound’s milieu. The hypertonicity of honey itself may also create a destructive environment around the tumor cells that ultimately causes cell shrinking.

Clinical and experimental studies about TI have become popular again after the reports about TSR$^{2-11}$ The mechanism of TSR, which is most likely a form of TI, remains unclear despite numerous studies.$^{2-8}$ Exfoliation of tumor cells due to tumor manipulation may lead to TI.$^{11,19}$ Jones et al$^3$ showed increasing amounts of the deposition of free intraperitoneal viable tumor cells into experimental trocar site wounds as local isolated recurrences. A scin-
tigraphic model confirmed the possible role of exfoliated cells.\textsuperscript{20} Contributing to the implantation of tumor cells may be pneumoperitoneum, carbon dioxide, increased abdominal pressure, the desufflation rate of pneumoperitoneum, and a chimney effect of carbon dioxide leakage around the trocars.\textsuperscript{2-8,19} Wu et al\textsuperscript{5} demonstrated that local treatment of abdominal wounds with povidone-iodine and silver sulfadiazine reduced TI. However, these agents do not accelerate wound healing, as does honey, and may in fact impair it. Local excision of trocar site wounds has also been shown to reduce TI.\textsuperscript{8} These factors affirm that local mechanisms may play a role in the formation of TSR. With this knowledge, local protection of wounds with a material that provides an effective barrier against wound invasion may prevent TSR. Presumably, the same principles are applicable to both TSR and TI in subcutaneous wounds. This is because the main factors that promote TI are surgical trauma and wound healing.\textsuperscript{21-23}

Honey has been used to accelerate wound healing since ancient times.\textsuperscript{12-14} Except for the presence of some clostridial spores, honey is sterile and highly bactericidal.\textsuperscript{12,24,25} \(\gamma\)-Irradiation sufficiently sterilizes honey when necessary.\textsuperscript{24} The wound healing and antimicrobial properties of honey may be attributed to its hypertonicity, low pH, and acceleration of epithelialization as well as the presence of inhibin, a thermolabile substance, and enzymes such as catalase.\textsuperscript{12-14,25} Honey also has a hygroscopic effect in reducing edema and constitutes a viscous barrier against wound invasion.\textsuperscript{12} Honey contains caffeic acid ester derivatives at levels of 20\% to 25\%.\textsuperscript{15} These compounds affect a broad spectrum of activities, including possible tumor inhibition.\textsuperscript{15,16} Topical application of honey on wounds leads to faster eradication of bacterial infections.\textsuperscript{26} The osmotic effects of honey appear to aid its antibacterial and antitumor activity.\textsuperscript{27}

Ehrlich ascites tumor was first derived from mammary cells of rats.\textsuperscript{28} Supply maintenance of this tumor is carried out in our research laboratory by weekly intraperitoneal injection in BALB/c mice. Subcutaneous injection of 8 \times 10^6 tumor cells in 0.5 mL of isotonic sodium chloride obtained from ascites of a tumor-bearing animal is adequate to establish solid TI (Figures 1 and 2). Ehrlich ascites tumor, which is highly invasive and transferable, can be used as a TI model in mice. In this study, TI formation was established in all control group animals. The application of honey interrupted TI when used before and after tumor inoculation.

Honey could be used on trocar wounds of patients with malignant disease to prevent TSR. It may also prevent infection with its bactericidal effects. Wound healing may even be enhanced with topical application of honey. Clinical use of honey on trocar wounds is not likely to cause any detrimental effects. Honey may also provide benefit in conventional oncological surgery where TI is predictable. However, metabolic effects of honey when used on large lesions are not known and need further investigation.
In conclusion, preventive covering of surgical wounds with honey seems to be a harmless procedure and may constitute at least a partial barrier that might overcome tumor cell invasion.

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Reprints: Ismail Hamzaoglu, MD, Department of Surgery, Cerrahpaşa Medical School, Istanbul University, E-2/3 A-934750, 5. Kisim Atakoğlu, Istanbul, Turkey (e-mail: hulya@turk.net).

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**Invited Critique**

The benefits of honey as a topical agent for wound healing were discovered thousands of years ago. This report of honey being used internally to reduce tumor implantation is another example in the literature of a renewed interest in the medicinal use of honey.

Honey is a complex hyperosmolar mixture of various sugars, and also possesses antimicrobial properties owing to the presence of hydrogen peroxide. Depending on the floral derivation of the pollen used in making the honey, its antimicrobial properties can be strengthened significantly. Other studies have suggested its efficacy in reducing the bacterial burden in an open wound.

Several small studies, including 2 prospective studies of burn patients, have reported the use of honey as a topical wound-healing agent. Two animal studies have demonstrated improved healing in open-wound models, and there is some anecdotal evidence suggesting the benefits of honey in treating chronic wounds. Aside from its antimicrobial effects, the mechanisms by which honey acts in wound healing have not been described. Additional beneficial properties need to be explored with further research.

In this study, a straightforward protocol was used, in which an ascites tumor was injected subcutaneously into a traumatized pocket, and then honey was added to the pocket, preventing tumor implantation. Although the authors conjecture that honey provided a physical barrier to implantation, it is possible that the tumor cells may have been killed by the hyperosmolar environment, as the significant inflammatory infiltrate seen histologically would indicate. Nevertheless, the honey was well tolerated and could be considered for coating a trocar to avoid tumor implantation. Further study is needed to establish safety and dosing for the internal application of honey, since the body of medical evidence demonstrates its topical use only.

Honey as a topical antibiotic agent has several efficient properties: it is natural, the risk of allergy is low, it has a broad antimicrobial spectrum, it tolerates and could be considered for coating a trocar to avoid tumor implantation. Further study is needed to establish safety and dosing for the internal application of honey, since the body of medical evidence demonstrates its topical use only.

**Thomas A. Mustoe, MD**

**Chicago, Ill**