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Healing Times for Circular Wounds on Plane and Spherical Bone Surfaces

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Abstract—A mathematical model is developed for the rate of healing of a circular wound in a spherical "skull". The motivation for this model is based on experimental studies of the "critical size defect" (CSD) in animal models; this has been defined as the smallest intraosseous wound that does not heal by bone formation during the lifetime of the animal [1]. For practical purposes, this timescale can usually be taken as one year. In [2], the definition was further extended to a defect which has less than ten percent bony regeneration during the lifetime of the animal. CSDs can "heal" by fibrous connective tissue formation, but since this is not bone, it does not have the properties (strength, etc.) that a completely healed defect would. Earlier models of bone wound healing [3,4] have focused on the existence (or not) of a CSD based on a steady-state analysis, so the time development of the wound was not addressed. In this paper, the time development of a circular cylindrical wound is discussed from a general point of view. An integro-differential equation is derived for the radial contraction rate of the wound in terms of the wound radius and parameters related to the postulated healing mechanisms. This equation includes the effect of the curvature of the (spherical) skull, since it is clear from the experimental evidence that the size of the CSD increases monotonically with the size of the calvaria. Certain special cases for a planar wound are highlighted to illustrate the qualitative features of the model, in particular, the dependence of the wound healing time on the initial wound size and the thickness of the healing rim.

Keywords—Wound healing, Critical size defect, Healing times, Radial contraction.

INTRODUCTION

The fields of bone regeneration and wound healing in general often rely on suitable animal models to test experimental bone and tissue repair materials. One accepted model for the former is the so-called *critical size defect* (CSD), which has been defined as the smallest intraosseous wound that does not heal by bone formation during the lifetime of the animal [1]. For practical purposes this timescale can usually be taken as one year. In [2], the definition was further extended to a defect which has less than ten percent bony regeneration during the lifetime of the animal. CSDs can "heal" by fibrous connective tissue formation, but since this is not bone, it does not have the properties (strength, etc.) that a completely healed defect would. Some typical CSDs are, for rat, rabbit, dog, and monkey calvaria (skullcap), respectively, 8 mm, 15 mm, 20 mm, and 15 mm (details can be found in [1]).

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Wound healing, when it occurs, does so by means of a combination of various processes. Chemotaxis (the movement of cells up a concentration gradient), neovascularization, synthesis of extracellular matrix proteins, and scar remodeling [5]. Growth factors are likely to play a very significant role in bone regeneration [6–9]. Such factors include transforming growth factor β (TGF-β), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), and in the case of skin, epidermal growth factor (EGF), [6,10]. Furthermore, the supply of oxygen to a wound has much influence on the quality of healing [7], and hence, angiogenesis is of vital significance in bone and tissue regeneration [11,12].

THE GROWTH EQUATION

We consider first the expression for the area of a circular disk of radius $\breve{R}$ on the surface of a sphere of radius $a > R$ (note that the radius $\breve{R}$ is measured across the two-dimensional surface and R is its plane projection on the r-θ plane). It is readily seen that the area $A(R)$ is given by the double integral

$$A(R) = \int_0^{2\pi} \int_0^R \frac{ar}{\sqrt{a^2 - r^2}}\, dr\, d\theta = 2\pi a \left(a - \sqrt{a^2 - R^2}\right), \tag{1}$$

which reduces to the the expected result $A(R) = \pi R^2$ in the limit as $R/a \to 0$.

It follows that if a circular wound shrinks from an initial radius $R(0)$ (i.e., at time $t = 0$) to radius $R(t)$ at time t, then the magnitude of the change in area Δ is

$$\Delta = 2\pi a \left(\sqrt{a^2 - R^2(t)} - \sqrt{a^2 - R^2(0)}\right). \tag{2}$$

We now consider the spherical skull to have a uniform relative thickness $h\,(\ll a)$ and write down an appropriate form for the conservation of volume as the wound heals (in a symmetrical manner). The total volume of healing that occurs as the wound radius decreases from $\rho(0)$ to $\rho(t)$ in time $t \geq 0$ must equal the total volume of bone produced in time $t \geq 0$, i.e., from (1) and (2),

$$\left(\sqrt{a^2 - R^2(t)} - \sqrt{a^2 - R^2(0)}\right) = \int_0^t \int_{R(t)}^{R(0)} \frac{rS(R(t), r)}{\sqrt{a^2 - r^2}}\, dr\, dt \tag{3}$$

(cancelling a factor $2\pi ah$ on both sides), where $S(R(t), r)$ is a term representing the rate of new bone growth as a function of position in the bone exterior to the wound. It is often the case that a "collar" of bone is produced in wounds as they heal; this additional thickening of bone in the vicinity of the wound can be incorporated into the model should it be considered necessary.

A more convenient form of this equation is obtained by differentiating with respect to time to give

$$\frac{dR^2}{dt} = -2\sqrt{a^2 - R^2} \int_{R(t)}^{R(0)} \frac{rS(R(t), r)}{\sqrt{a^2 - r^2}}\, dr. \tag{4}$$

Note from equation (1) the interesting (dimensional) result that

$$A - \pi R^2 = \frac{A^2}{4\pi a^2}, \tag{5}$$

i.e., the difference in area between the circular wound on the spherical surface and its circular projection on a plane is the square of the "curved" wound area divided by the area of the sphere (or spherical skull).

Let us consider the special case of the limiting plane surface, i.e., as R/a and r/a become small. In this limit, the equation of conservation of volume (4) becomes

$$\frac{dR^2}{dt} = -2 \int_{R(t)}^{R(0)} rS(R(t), r)\, dr. \tag{6}$$

We choose expressions for $S(R(t), r)$ that are expected to be reasonable qualitative descriptions of the healing process in wounds, namely attaining a maximum at the wound edge and decreasing away from that edge. Since no further healing is necessary once $R(t) = 0$, there is a restriction that $S(0, r) = 0$ (note that $R(t) \le r \le R(0)$). Analytical (where possible) and numerical results for the more general case governed by equation (4) will be presented elsewhere.

MODEL I

If the growth of new bone is confined to a ring of constant width d such that

$$S(R, r) = \begin{cases} \dfrac{S_0 R}{R(0)} \left(1 + \dfrac{R - r}{d}\right), & R \le r \le R + d, \\ 0, & \text{otherwise}, \end{cases} \tag{7}$$

where $R = R(t)$ and S_0 is a constant reference healing rate. Note that $S(R, R) = S_0 R / R(0)$, $S(R, R+d) = 0$, and $S(0, r) = S(0, 0) = 0$. This last condition, for $r = R = 0$ is a very reasonable one because it is to be expected that the rate of new bone growth will decrease as the healing process draws to a close. Then from equation (6),

$$\frac{dR^2}{dt} = -\frac{1}{3} \frac{S_0 R}{R(0)} d\,(3R + d)\,, \tag{8}$$

whence

$$R(t) = \left[R(0) + \frac{d}{3}\right] e^{-S_0 dt / 2R(0)} - \frac{d}{3}, \tag{9}$$

from which the healing time t_h, defined by $R(t_h) = 0$, is

$$t_h = \frac{2R(0)}{S_0 d} \ln\left(\frac{3R(0)}{d} + 1\right). \tag{10}$$

Note that for given $R(0)$, t_h is a monotone decreasing function of d, and for given d, t_h is a monotone increasing function of $R(0)$.

MODEL II

In this model, we consider a simpler functional form for $S(R, r)$ but allow the active wound rim $[R, R + d]$ to be variable, i.e., $d = d(R)$. Specifically,

$$S(R, r) = \begin{cases} \dfrac{S_0 R}{R(0)}, & R \le r \le R + d(R), \\ 0, & \text{otherwise}, \end{cases} \tag{11}$$

where

$$d = \alpha R(0) + \beta R, \qquad \alpha \ge 0, \quad \beta > 0, \tag{12}$$

which allows larger wounds to have larger healing rims. After some reduction based on equation (6), it is found that

$$\frac{dR}{dt} = -\frac{S_0 \beta(\beta + 2)}{2R(0)} \left[\left(R + \frac{\alpha(1 + \beta)}{\beta(\beta + 2)}\right)^2 - \left(\frac{\alpha}{\beta(\beta + 2)}\right)^2\right]. \tag{13}$$

Again, after some reduction, this has solution

$$R(t) = \frac{R(0)\alpha/(\beta + 2)\left[(\alpha + \beta + 2)/(\alpha + \beta) e^{-\alpha S_0 t} - 1\right]}{\left[1 - ((\alpha + \beta + 2)/(\alpha + \beta))(\beta/(\beta + 2)) e^{-\alpha S_0 t}\right]}, \tag{14a}$$

from which it follows that

$$t_h = \frac{1}{\alpha S_0} \ln \left(\frac{\alpha + \beta + 2}{\alpha + \beta} \right). \tag{15a}$$

Since $d(R(0)) = (\alpha + \beta)R(0)$, these last two equations may be written in a more biologically appealing way as

$$R(t) = \frac{R(0)\alpha/(\beta+2) \left[(1 + 2R(0)/d(0))\, e^{-\alpha S_0 t} - 1 \right]}{\left[1 - (1 + 2R(0)/d(0))\, (\beta/(\beta+2))\, e^{-\alpha S_0 t} \right]} \tag{14b}$$

and

$$t_h = \frac{R(0)}{S_0 d(0)} \ln \left(1 + \frac{2R(0)}{d(0)} \right), \tag{15b}$$

where $d(0)$ is the thickness of the rim when $R = 0$ (*not* when $t = 0$). As in Model I, for given $R(0)$, t_h is a monotone decreasing function of $d(0)$ (the minimum thickness of the healing rim which occurs when $R = 0$), and for given $d(0)$, t_h is a monotone increasing function of $R(0)$. It appears from these two models that the healing times are relatively insensitive to the detailed functional form of the growth rate function, but that the ratio of the initial wound size to the healing rim thickness is crucial to whether or not a CSD occurs. To see this, note that if $R(0)/d(0)$ is large enough, then certainly $t_h > T$, where T is the lifetime of the animal. Certainly, some healing may occur in cases of CSDs (and this is observed in animal models), but not enough to close the wound in the time available.

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