

Effect of absorbable topical hemostatic agents on the relaxation time of blood: an in vitro study with implications for postoperative magnetic resonance imaging

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Object. Absorbable topical hemostatic agents are commonly used in neurosurgery. In this study the authors examine the longitudinal relaxation time (T_1) of blood in contact with these agents over time, measured in vitro, to determine if their presence could affect the interpretation of postoperative magnetic resonance (MR) images.

Methods. Coagulated and anticoagulated blood were used, both oxygenated and deoxygenated. The effects of a collagen-based agent (Collastat) and a cellulose-based agent (Surgicel) on the pH and T_1 values of blood and on those of saline (used as a control) were investigated. The T_1 was measured as a function of magnetic field strength and time by using a field-cycling relaxometer. This instrument measures $1/T_1$, the rate of T_1 , from which the T_1 value is computed. The T_1 values of blood were compared with those of hemostat-induced blood clots and with those of both gray and white matter of the brain. Signal changes on T_1 -weighted MR images were predicted on the basis of altered T_1 values in vitro. Postoperative images were visually examined for the predicted changes. With the addition of Surgicel, blood had decreased pH and significantly shortened T_1 at all fields, essentially within minutes, although it affected the T_1 of saline only minimally. The effect of Surgicel increasingly shortened the T_1 for 4 days in oxygenated blood. Collastat had no significant effect. The presence of some paramagnetic methemoglobin in Surgicel-induced clots was demonstrated using the relaxometer at a time when diamagnetic oxyhemoglobin would be present in naturally occurring blood clots. A bright signal that could mimic residual tumor on contrast-enhanced images was predicted and confirmed on postoperative T_1 -weighted MR images obtained in patients in whom Surgicel lined the tumor bed. It was not present in cases in which Surgicel was not used.

Conclusions. Surgicel alters the appearance of early postoperative MR images. To avoid misinterpretation, clinicians should be aware of this phenomenon.

KEY WORDS • absorbable hemostatic agent • oxidized regenerated cellulose • magnetic resonance imaging

ABSORBABLE topical hemostatic agents are used in all surgical specialties to achieve hemostasis. Some of these agents are collagen based (microfibril or sponge) and others are gelatin or cellulose based. Which agent is used in a particular surgical intervention depends on many factors, including ease of application, bioabsorption, antigenicity, and tissue reaction.

In the present in vitro study we investigated the effect of absorbable hemostatic agents on the proton T_1 of blood.²² We hypothesized that these agents may alter the proton T_1 of clotting blood and the time course of these durations. Thus, the presence of absorbable hemostatic agents might affect the interpretation and optimal timing of postoperative MR images because blood products in the surgical bed may produce altered MR signal characteristics.

The effects of a collagen-based sponge (Collastat) and oxidized regenerated cellulose (Surgicel) on the T_1 of blood and saline (used as a control) and on the time course of T_1

as a function of magnetic field strength were investigated. Our goal was twofold: 1) to compare the T_1 values of coagulated and anticoagulated blood with those of hemostat-induced blood clots and with those of gray and white matter of the brain;¹⁶ and 2) to evaluate the implications of these in vitro data for timing and interpretation of in vivo postoperative MR images.

Materials and Methods

After approval for the study had been obtained from the internal review board of New York Medical College, venous blood was drawn from a healthy human volunteer who had not ingested any platelet-active drugs during the previous 10 days. The fasting value of the hematocrit, hemoglobin concentration, red and white blood cell counts, and sedimentation rate were determined by routine clinical analysis. Blood was collected either in a vacutainer containing sodium heparin as the anticoagulant (Becton Dickinson Vacutainer Systems, Franklin Lakes, NJ) or in a test tube and used fresh immediately. As the blood clotted and the clot retracted, serum was removed by blotting with absorbent paper. For clinical relevance, whole blood was studied while fully oxygenated (kept in an atmosphere of 95% oxygen/5% carbon dioxide) as well as while fully oxygenated and anticoagulated. To elucidate different relaxation

Abbreviations used in this paper: MR = magnetic resonance; NMRD = nuclear magnetic relaxation dispersion; T_1 = longitudinal relaxation time; $1/T_1$ = longitudinal relaxation rate; T_2 = transverse relaxation time.

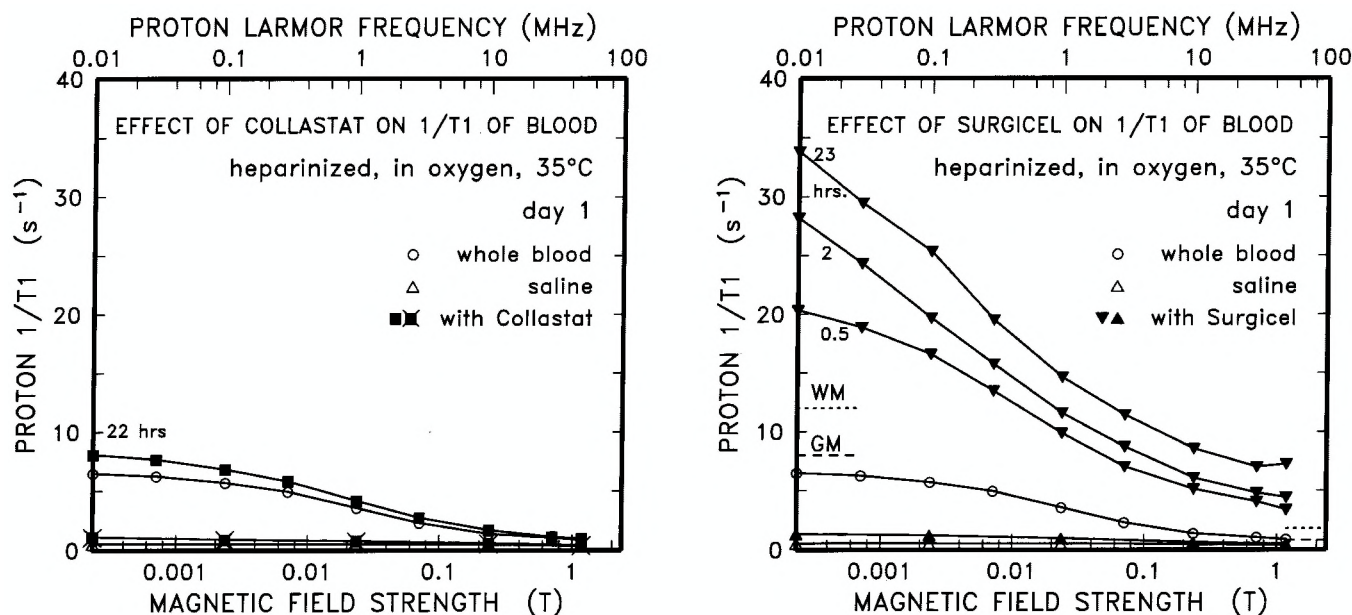


FIG. 1. Graphs demonstrating $1/T_1$ NMRD profiles, at 35°C, of 0.6 ml of heparinized, oxygenated human whole blood and saline before and after exposure to a 20-mg collagen-based sponge (Collastat; *left*) or 75 mg of oxidized regenerated cellulose (Surgicel; *right*). The time, in hours after the hemostatic agents were added, is indicated to the right of the ordinate. Collastat increased the $1/T_1$ value of blood only slightly, whereas Surgicel caused a rapid increase in the values of $1/T_1$ at all fields. The dotted and dashed lines (*right*) indicate the low- and high-field values of $1/T_1$ for human white matter (WM) and gray matter (GM) of the brain (Koenig, et al., 1990). Note that the lines of the $1/T_1$ NMRD profiles simply connect the data points and should not be interpreted as an exact fit to the data.

contributions, blood was studied after it had been both deoxygenated and completely reduced (by addition of 5 mg Na-dithionite/ml blood³ and kept in an atmosphere of nitrogen), and deoxygenated and anticoagulated.

Two commercially available absorbable topical hemostatic agents were used: a collagen-based sponge (Collastat; Vitaphore Wound Healing, Inc., Chicago, IL) and oxidized regenerated cellulose (Surgicel; Ethicon, Johnson & Johnson, Somerville, NJ). Twenty milligrams of Collastat or 75 mg of Surgicel were added in vitro to 0.6 ml of human whole blood or physiological saline. These amounts were found to be sufficient to gel the sample volume homogeneously and to minimize multiexponential proton relaxation.

The inverse of the proton T_1 , termed the "longitudinal relaxation rate" or $1/T_1$, was measured as a function of magnetic field strength over the field range of 0.24 mT to 1.2 T (corresponding to a range of 0.01 to 50 MHz proton Larmor frequency) by using a field-cycling relaxometer. Using this instrument, the $1/T_1$ can be measured at low field strengths with a high field sensitivity.^{12,14} The resulting profiles are known as $1/T_1$ NMRD profiles. Because the longitudinal relaxation rates ($1/T_1$), but not the longitudinal relaxation times (T_1), are additive for different relaxation contributions, we used the former in this study. Each reported value of $1/T_1$ represents the fit of a single exponential to the magnetization data, with the error of this fit recorded as well. To minimize multiexponential relaxation, red blood cells in anticoagulated blood had to be prevented from settling during the measuring time by gently moving such samples approximately every 5 minutes.

The $1/T_1$ NMRD profiles were followed in vitro for all samples over a period of 3 weeks, the amount of time it takes in vivo for fresh blood to evolve from the acute phase through the subacute phase to the chronic phase. To evaluate the implications of the $1/T_1$, measured in vitro for postoperative MR images, we used data generated during the first 4 days. Changes in signal intensity on T_1 - and T_2 -weighted images were predicted from changes in the $1/T_1$ at the highest and lowest field strengths of the relaxometer, respectively. (Note that the $1/T_1$ measured at the lowest field is related to the $1/T_2$ measured at imaging fields.¹³ A high value of $1/T_1$ at low fields correlates with shortening of the T_2 and a darker signal on T_2 -weighted

MR images; a high value of $1/T_1$ at high fields results in signal brightness on T_1 -weighted images). Signal changes, predicted on the basis of the in vitro $1/T_1$, were compared with those visually observed on MR images of naturally occurring blood clots^{8,9} in vivo and on postoperative MR images obtained in patients from whom tumors had been excised, with and without placement of hemostatic agents in the tumor bed.

The samples of blood and saline, with or without addition of hemostatic agents, were kept in an atmosphere of oxygen or nitrogen gas in tightly stoppered test tubes at 35°C. The pH was measured using a pH meter (Thermo Orion, Beverly, MA) before and 15 minutes after addition of the hemostatic agents. To determine the influence of a low pH on the $1/T_1$ NMRD profile of blood, the pH of one sample was adjusted with hydrochloric acid to the low pH value of blood in contact with Surgicel before the $1/T_1$ was measured.

Results

Proton Relaxation in Blood Containing Hemostatic Agents

The effect of a 20-mg collagen-based sponge (Collastat) or 75 mg of the oxidized regenerated cellulose (Surgicel) on the $1/T_1$ of 0.6 ml of blood or saline was investigated as a function of magnetic field strength and time. The addition of Surgicel increased the $1/T_1$ of oxygenated blood significantly at all fields, essentially within minutes, although it increased the $1/T_1$ of saline only minimally. By contrast, Collastat increased the $1/T_1$ of both blood and saline only slightly. These qualitatively different effects of Surgicel and Collastat on the $1/T_1$ values were observed in both coagulated and anticoagulated blood; but the difference was best demonstrated in anticoagulated blood, which has a constant water content and $1/T_1$ during the first 24 hours because the blood does not clot.

The effects of Collastat and Surgicel on the $1/T_1$ values

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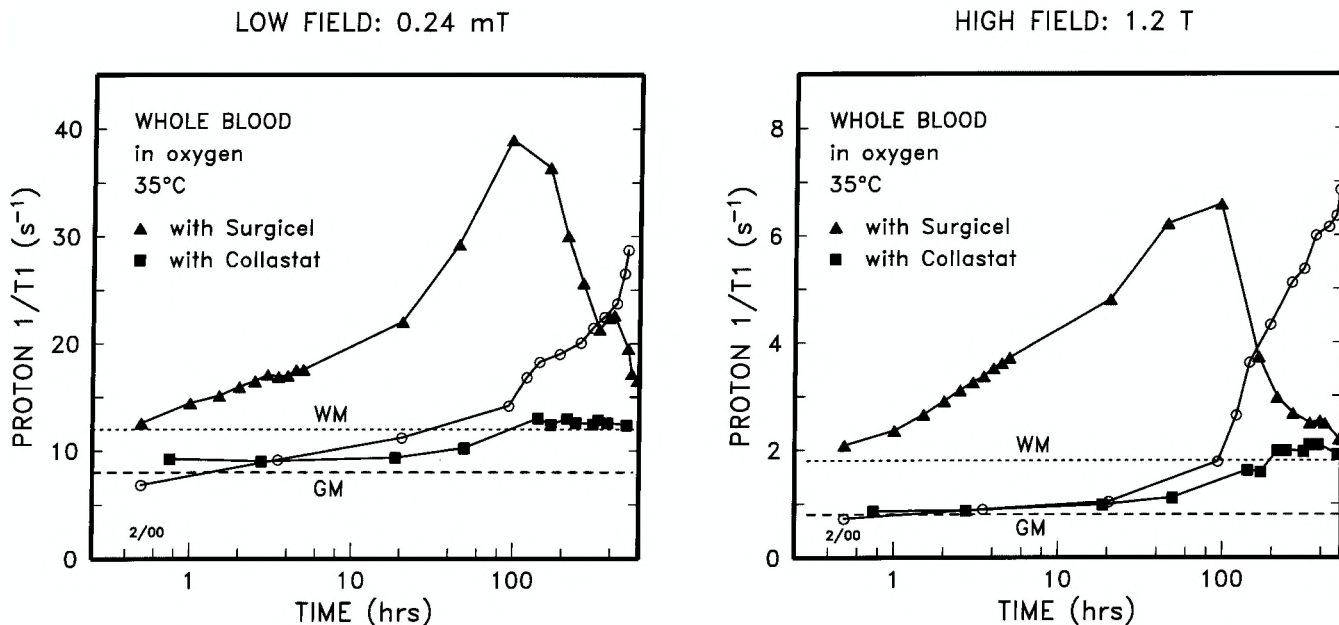


FIG. 2. Graphs depicting the values of $1/T_1$ at the lowest (0.24 mT, *left*) and highest (1.2 T, *right*) field strengths of the relaxometer plotted against time for 0.6 ml of oxygenated, human whole blood without hemostatic agents (*open circles*) and after addition of 75 mg of Surgicel or 20 mg of Collastat. During the first 4 days, the $1/T_1$ values of the Collastat-induced blood clot are comparable to those of a naturally occurring blood clot, whereas those of the Surgicel-induced clot are higher. The $1/T_1$ values are shown for both white matter and gray matter of the brain.

of anticoagulated whole blood and saline were determined as a function of magnetic field strength (Fig. 1). The profiles of Collastat and blood were essentially additive and, therefore, no interactions occurred. By contrast, the profiles of Surgicel and blood were not additive. With Surgicel an interaction must have occurred within the first 0.5 hour. Furthermore, the shape of the $1/T_1$ NMRD profile of the Surgicel-induced blood clot (Fig. 1 *right*) changed within the first 2 hours, indicating a transition from mostly rotationally mobile (0.5-hour profile) to immobilized protein (2-hour profile).¹⁴ The errors in the $1/T_1$ values of saline were 0.5 to 0.8%, those of blood 0.6 to 1.2%, and those of the Collastat-induced clot 0.7 to 1.5%, depending on field strength. For the Surgicel-induced clot the error of the fit to a single exponential $1/T_1$ ranged between 2% and 4.5%, indicating multiexponential proton relaxation.

The time courses of the $1/T_1$ values at the lowest and highest field strengths measured by the relaxometer were determined for fully oxygenated, coagulated whole blood in vitro, with and without addition of hemostatic agents (Fig. 2). The $1/T_1$ values of the Collastat-induced clot and the naturally occurring blood clot were comparable at both low and high fields and were similar to those of gray matter of the brain during Day 1, increasing to those of white matter during the next 3 days. By contrast, the $1/T_1$ values of the Surgicel-induced clot were significantly higher; starting with white matter rates, they increased steadily at both low and high fields, on Day 4 reaching values that a fully retracted naturally occurring blood clot without hemostatic agents would approach only after 3 weeks in this in vitro experiment.

The pH of Blood Containing Hemostatic Agents

When 20 mg of Collastat was added to 0.6 ml of fresh

human blood, the pH changed from 7.45 ± 0.1 to 7.4 ± 0.2 in nonheparinized blood and from 7.5 ± 0.1 to 7.2 ± 0.2 in heparinized blood (3 samples each). When 75 mg of Surgicel was added to 0.6 ml of blood, the pH dropped to 3.7 ± 0.1 in nonheparinized blood (six samples) and to 3.9 ± 0.1 in heparinized blood (three samples). Collastat reduced the pH of saline and heparinized saline by only 0.2, whereas Surgicel reduced the pH of saline from 5.5 to 1.3 and the pH of heparinized saline from 6.8 to 1.7. Thus, in the amounts used, oxidized regenerated cellulose (Surgicel) lowered the pH of blood and, even more so, of saline significantly, whereas the collagen-based fleece (Collastat) did not.

Interaction of Blood and Surgicel

When the $1/T_1$ NMRD profile of human oxygenated whole blood was measured after the pH was adjusted to the same low value of the Surgicel-induced blood clot (pH 4), it was found that the low pH accounted for 50% of the initial increase in the $1/T_1$ at the high field (0.5-hour profile; Fig. 1 *right*), but did not increase the $1/T_1$ at the low field significantly. The high-field values of the $1/T_1$ of the Surgicel-induced clot could be explained by a paramagnetic relaxation contribution from methemoglobin during Day 1. To test this hypothesis, four Surgicel-induced blood clots were prepared: 75 mg of Surgicel gauze was added to each of two 0.6-ml samples of fully oxygenated whole blood (kept in an oxygen atmosphere) and to two samples of fully reduced, deoxygenated blood (reduced by addition of 5 mg Na-dithionite/ml blood,³ and kept in a nitrogen atmosphere). One sample in each group was heparinized. Because only diamagnetic oxyhemoglobin can oxidize to paramagnetic methemoglobin, the rate increase

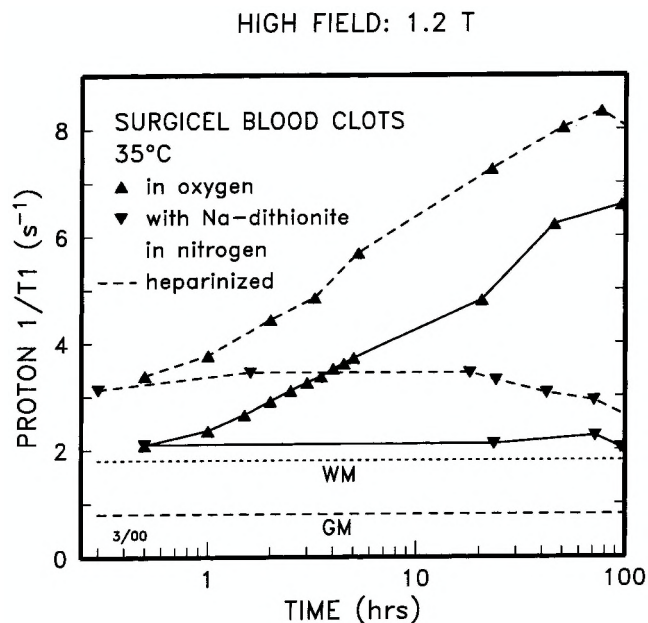


FIG. 3. Graph demonstrating the values of $1/T_1$ at the highest field strength of the relaxometer (1.2 T) plotted against time (first 4 days) for four Surgicel-induced blood clots: two clots with fully oxygenated blood, kept in an atmosphere of 95% oxygen/5% carbon dioxide and two clots with completely deoxygenated blood, which was reduced by addition of 5 mg Na-dithionite/ml blood and kept in a nitrogen atmosphere. Heparinized blood was used for one sample in each group. The $1/T_1$ increases progressively in the oxygenated Surgicel-induced clots, but not in the deoxygenated clots. The $1/T_1$ values are shown for both white and gray matter of the brain (Koenig, et al., 1990).

caused by interaction with Surgicel at the high field was expected to be much larger in oxygenated blood than in fully reduced, deoxygenated blood. These predictions were confirmed.

Figure 3 shows the value of $1/T_1$ at 1.2 T, the highest field strength of the relaxometer, plotted against time, for two oxygenated and two reduced, deoxygenated Surgicel-induced blood clots (one clot of each group was heparinized). The $1/T_1$ increased steadily during the first 4 days in the oxygenated Surgicel-induced clots, whereas no such increase occurred in the completely reduced, deoxygenated clots. An almost constant increase in the $1/T_1$ appeared in both heparinized samples when compared with the $1/T_1$ values of the corresponding nonheparinized samples, suggesting that heparin may also interact with Surgicel. When Surgicel was added to partly deoxygenated blood (< 2.5 mg of Na-dithionite/ml blood,³ and kept in a nitrogen atmosphere), the $1/T_1$ increased with a variable time course (data not shown).

Implications for Interpretation of MR Images

Signal intensities of blood clots with and without addition of hemostatic agents were estimated for T_2 - and T_1 -weighted MR images from the $1/T_1$ values shown in Fig. 2. From these data one predicts the occurrence of a hypo- to isointense signal when compared with that of brain for the naturally occurring blood clot, as observed in intracranial hematomas,^{8,9} and for the Collastat-induced clot, but

an increasing hypointense signal on T_2 -weighted and an increasing hyperintense signal on T_1 -weighted MR images for the Surgicel-induced clot during Days 1 through 4. Visual inspection of postoperative images, which were obtained 24 to 48 hours after surgery for intracranial tumors in two patients, revealed the bright signal predicted on T_1 -weighted images when Surgicel was used (Fig. 4 lower).

The preoperative sagittal image of a large right cerebellar tumor in a 23-month-old girl after injection of contrast agent is shown in Fig. 4 upper left. Postoperative images were obtained before and after injection of contrast agents 24 hours after gross-total resection of a large pilocytic astrocytoma (Fig. 4 upper center and upper right). For this patient, the surgeon used no absorbable hemostatic agents. Postoperative coronal images were obtained before and after injection of contrast agents 30 hours after gross-total resection of a left occipital metastatic carcinoma in a 52-year-old man (Fig. 4 lower). For this patient, the surgeon lined much of the tumor bed with Surgicel gauze, resulting in the appearance of a bright rim around most of the resection cavity on early T_1 -weighted postoperative images (Fig. 4 lower left). After injection of contrast agent, no additional enhancement was noted on the T_1 -weighted images of either patient, confirming gross-total resection. The T_2 -weighted images were unrevealing.

Discussion

Hemostatic Agents in Blood

All topical hemostatic agents primarily aid the quick formation of an occlusive plug. The efficacy of different hemostatic agents has been evaluated in animals,^{1,5,6,21,25} and tissue responses have been reported for a variety of sites.^{7,18,19,24} In *in vivo* studies of hemostatic efficacy, collagen-based agents have generally proved superior to gelatin- and cellulose-based agents, despite different handling characteristics.^{1,11,20,24} Comparative *in vitro* studies yielded a similar overall ranking: collagen-based agents (sponges or microfibrils) exceeded Gelfoam, which in turn worked more effectively than oxidized regenerated cellulose (Surgicel).²³

Oxidized regenerated cellulose (Surgicel), a homogeneous soft knitted gauze, is the absorbable topical hemostatic agent preferred in cranial surgery. Its chemical composition consists of polyanhydroglucuronic acid manufactured from pure alpha cellulose. The primary alcohol at C6 has been oxidized to a carboxyl group.¹⁷ By weight, more than 15% of Surgicel is acid. Bjorensen, et al.,² documented a significant decrease in the pH of heparinized blood, plasma, and serum after contact with Surgicel; and these findings are supported by data presented in the present study. The reduction in pH is less dramatic in blood than in saline because of buffering proteins. Surgicel liberates hemoglobin from red blood cells and removes calcium ions from solution. The hemoglobin and calcium unite chemically with the cellulose fibers of the gauze.¹⁷ Presumably because of its acidity, Surgicel can cause inflammatory reactions.²

The collagen-based sponge (Collastat) is a nonwoven sheet and is much denser than Surgicel; the sponge has small and large pores ($\leq 100 \mu\text{m}$) separated by ridges of collagen material. It is native collagen obtained from

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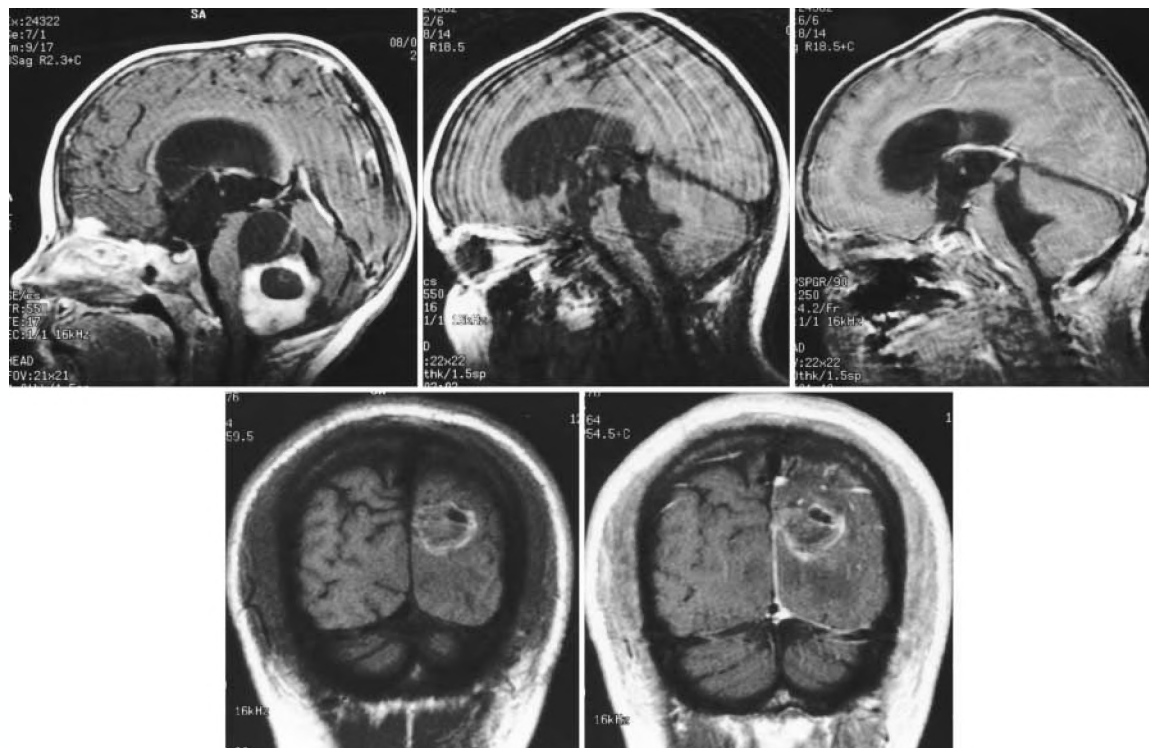


FIG. 4. *Upper Left:* Preoperative contrast-enhanced T₁-weighted sagittal MR image demonstrating a large cerebellar pilocytic astrocytoma in a 23-month-old girl. *Upper Center and Upper Right:* Postoperative T₁-weighted MR images obtained before and after administration of gadolinium, respectively, 24 hours after gross-total resection in the same patient. No absorbable hemostatic agents were used during surgery. *Lower Left and Lower Right:* Postoperative T₁-weighted coronal images obtained 30 hours after gross-total resection of a left occipital metastatic carcinoma in a 52-year-old man. Both the unenhanced (*lower left*) and contrast-enhanced (*lower right*) studies demonstrate a hyperintense signal at the rim of the tumor bed, which was lined with Surgicel after tumor resection. No additional enhancement was noted on postoperative contrast-enhanced images obtained in either patient.

bovine tendon, and is used extensively for parenchymal bleeding throughout a wide area. It is debatable whether equal volumes, weights, or surface areas of hemostatic agents should be used in comparative *in vitro* studies. In the present investigation, to gel an equal volume of blood or saline the amount of Surgicel required was 3.75-fold larger by weight than that of Collastat. A homogeneous sample volume is required for characterization of a system by a single exponential $1/T_1$ when measured using a relaxometer.

Proton Relaxation in Blood With and Without Addition of Hemostatic Agents

Proton relaxation in blood is dominated by the contribution of hemoglobin in red blood cells. In fresh blood, hemoglobin is present primarily as diamagnetic oxyhemoglobin, which evolves during later phases of blood clotting into paramagnetic methemoglobin.¹⁰ Blood clotting in the test tube varies significantly with experimental conditions, resulting in different levels of clot retraction. The addition of sodium heparin, a highly negatively charged, conjugated polysaccharide, to fresh blood completely prevents clotting *in vitro* as it does *in vivo*. Relaxation rates of anticoagulated whole blood were identical to those of freshly drawn blood.

Collastat and Surgicel exerted qualitatively and quantitatively different effects on the magnetic field dependence of the $1/T_1$ of anticoagulated blood, even when the 3.75-fold larger amount of Surgicel was taken into account (Fig. 1). No interaction detectable by water protons occurred between Collastat and blood; the $1/T_1$ NMRD profiles were additive and did not change during Day 1. Hemoglobin, presumably present as oxyhemoglobin in the Collastat-induced clot (no paramagnetic T₁ shortening was noted at high fields), remained rotationally mobile. By contrast, the $1/T_1$ of the Surgicel-induced clot changed rapidly as a function of magnetic field strength and time during Day 1. Interactions between this hemostatic agent and blood occurred, were detectable by water protons, and affected their $1/T_1$ dramatically. The magnitude of the $1/T_1$ NMRD profiles of the Surgicel-induced clot at the high field (Fig. 1 *right*) and the much larger error measured for the $1/T_1$ of the Surgicel-induced clot could be explained by some paramagnetic hemoglobin already present on Day 1, along with diamagnetic oxyhemoglobin. In addition, the shape of the $1/T_1$ NMRD profile changed within 2 hours from that of rotationally mobile hemoglobin, bending over at low fields and dispersing at high fields, to a dispersion profile characteristic for immobilized protein¹⁴ (polymerized, crosslinked, denatured protein) or tissue¹²⁻¹⁴ with

monotonically increasing low field rates. This finding is consistent with reported lysing of red blood cells and hemoglobin binding to Surgicel.¹⁷

The $1/T_1$ values for oxygenated nonanticoagulated fresh blood were time dependent, as expected (Fig. 2). As the blood clotted, the clot retracted, and the serum was removed; the hematocrit increased steadily, reaching its final concentration (almost double its initial value of 37.9%) after 23 hours. The $1/T_1$ increased accordingly, especially at low fields, at which the $1/T_1$ is proportional to the protein concentration.^{4,12-14} At Days 4 through 8, the $1/T_1$ increased at all fields, but most prominently at high fields, indicating the presence of paramagnetic hemoglobin.^{10,15} The ratio of the low-field to the high-field value of the $1/T_1$ on Day 8 indicates that it is not pure paramagnetic hemoglobin (methemoglobin),¹⁵ but a mixture of paramagnetic and diamagnetic hemoglobin present during the subacute phase in a fully retracted blood clot in vitro. The time dependence of the low field and high field $1/T_1$ values of blood in the presence of hemostatic agents (Fig. 2) can be summarized from the perspective of water protons: Collastat appears to inhibit the formation of paramagnetic methemoglobin (essentially no increase in $1/T_1$ values during the subacute phase; Fig. 2 right), whereas Surgicel appears to speed up oxidation of oxyhemoglobin to methemoglobin (increased $1/T_1$ values already present during the acute phase; Fig. 2 right). Based on measurements obtained with the relaxometer, the proof that indeed some diamagnetic oxyhemoglobin transforms into paramagnetic methemoglobin, essentially within the first half hour when oxygenated blood comes in contact with Surgicel, is shown in Fig. 3. This proof depended on showing that exposure to Surgicel does not result in increased high field $1/T_1$ when the hemoglobin in blood is present only as deoxyhemoglobin, as it is in completely reduced blood in a nitrogen atmosphere. The increase in $1/T_1$ in heparinized Surgicel-induced blood clots, both oxygenated and deoxygenated, compared with those in the respective nonheparinized samples (Fig. 3) may be caused by a possible complex formed by heparin with blood proteins and Surgicel.

Implications for the Interpretation of MR Images

The time course of signal intensities of intracranial hemorrhage (from the acute phase through the subacute and on to the chronic phase) on T_1 - and T_2 -weighted MR images can be used to date a hemorrhage. The evolution of intracellular diamagnetic oxyhemoglobin into paramagnetic deoxyhemoglobin and methemoglobin, accompanied or followed by cell lysis and, eventually, hemosiderin accumulation in granulocytes at the periphery,¹⁰ affects the $1/T_1$ of blood,¹⁰ which determines the contrast between intracranial hemorrhage and surrounding tissue in vivo. After surgical resection of a brain tumor, postoperative MR images are often obtained to assess the extent of resection and to estimate residual tumor volume. Adjuvant therapy may be recommended on the basis of these images. The timing of postoperative MR imaging is chosen so that blood clots appear hypo- to isointense when compared with surrounding brain, and surgical site inflammation is minimal. On injection of contrast agent within 24 to 48 hours after surgery, ideally only residual tumor will enhance. On the basis of the data from the present study, we predict a bright signal

on early postoperative T_1 -weighted MR images obtained in patients in whom Surgicel is used to line the tumor bed, resulting from the almost instant increase in the $1/T_1$ of blood in contact with Surgicel. Figure 4 lower left demonstrates that predictions made on the basis of these in vitro data hold true for in vivo MR images. The results of this in vitro study exaggerate what may happen in vivo, in which blood clots differently and the acidity induced by Surgicel would be diluted. But low pH alone does not account for the large increase in the $1/T_1$ of blood in contact with Surgicel; instead, the time course of the $1/T_1$ of clotting blood, which we described earlier, has been altered by the early presence of some paramagnetic hemoglobin, which binds to Surgicel at a time when diamagnetic intracellular oxyhemoglobin would be present in the acute blood clot without Surgicel.

The radiologist in clinical practice usually does not know whether an absorbable topical hemostatic agent was used during surgery, let alone which one. We have shown that, in addition to areas with a disrupted or injured blood-brain barrier, such as residual tumor or inflammatory lesions, Surgicel-induced blood clots have a bright appearance on early postoperative T_1 -weighted MR images obtained after administration of contrast agents. Thus, in cases in which subtraction of the signal before and after addition of contrast agent cannot be done accurately, residual tumor volume may be overestimated.

Conclusions

Different absorbable topical hemostatic agents affect the $1/T_1$ of blood, its magnetic field dependence, and its time course differently. When an altered $1/T_1$ results in signal intensities that can mimic disease, as is the case when Surgicel interacts with blood, the interpretation of postoperative MR images may be affected. Communication between the surgeon and radiologist concerning cases in which such an absorbable agent is used is essential to avoid the possibility of image misinterpretation.

Disclosure

The authors have no financial interest in any of the companies or products described in this paper.

References

1. Abbott WM, Austen WG: The effectiveness and mechanism of collagen-induced topical hemostasis. *Surgery* **78**:723-729, 1975
2. Bjorenson JE, Grove HF, List MG Sr, et al: Effects of hemostatic agents on the pH of body fluids. *J Endod* **12**:289-292, 1986
3. Briley-Sæbø K, Bjørnerud A: Accurate de-oxygenation of *ex vivo* whole blood using sodium dithionite. *Proc Intl Soc Magn Reson Med* **8**:2025, 2000 (Abstract)
4. Bryant RG, Marill K, Blackmore C, et al: Magnetic relaxation in blood and blood clots. *Magn Reson Med* **13**:133-144, 1990
5. Chvapil M, Owen JA, DeYoung DW: A standardized animal model for evaluation of hemostatic effectiveness of various materials. *J Trauma* **23**:1042-1047, 1983
6. Coln D, Horton J, Ogden ME, et al: Evaluation of hemostatic agents in experimental splenic lacerations. *Am J Surg* **145**:256-259, 1983
7. Finn MD, Schow SR, Schneiderman ED: Osseous regenera-

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- tion in the presence of four common hemostatic agents. **J Oral Maxillofac Surg** **50**:608–612, 1992
8. Gomori JM, Grossman RI, Goldberg HI, et al: Intracranial hematomas: imaging by high-field MR. **Radiology** **157**:87–93, 1985
 9. Gomori JM, Grossman RI, Hackney DB, et al: Variable appearances of subacute intracranial hematomas on high-field spin-echo MR. **AJNR** **8**:1019–1026, 1987
 10. Gomori JM, Grossman RI, Yu-Ip C, et al: NMR relaxation times of blood: dependence on field strength, oxidation state, and cell integrity. **J Comput Assist Tomogr** **11**:684–690, 1987
 11. Hait MR, Robb CA, Baxter CR, et al: Comparative evaluation of Avitene microcrystalline collagen hemostat in experimental animal wounds. **Am J Surg** **125**:284–287, 1973
 12. Koenig SH, Brown RD III: Field-cycling relaxometry of protein solutions and tissue: implications for MRI. **Prog NMR Spectr** **22**:487–567, 1990
 13. Koenig SH, Brown RD III: Relaxometry of solvent and tissue protons: diamagnetic contributions, in Partain CL, Price RR, Patton JA, et al (eds): **Magnetic Resonance Imaging**, ed 2. Philadelphia: WB Saunders, 1988, Vol 2, pp 1035–1048
 14. Koenig SH, Brown RD III: Relaxometry of tissue, in Gupta RK (ed): **NMR Spectroscopy of Cells and Organisms**. Boca Raton: CRC Press, 1987, Vol 2, pp 75–114
 15. Koenig SH, Brown RD III, Lindstrom TR: Interactions of solvent with the heme region of methemoglobin and fluoro-methemoglobin, in Ho C, Eaton WA, Collman JP, et al (eds): **Hemoglobin and Oxygen Binding**. New York: Elsevier Biomedical, 1982, pp 377–385
 16. Koenig SH, Brown RD III, Spiller M, et al: Relaxometry of brain: why white matter appears bright in MRI. **Magn Reson Med** **14**:482–495, 1990
 17. Miller JM, Jackson DA, Collier CS: An investigation of the chemical reactions of oxidized regenerated cellulose. **Exp Med Surg** **19**:196–202, 1961
 18. Olson RAJ, Roberts DL, Osbon DBA: A comparative study of polylactic acid, Gelfoam, and Surgicel in healing extraction sites. **Oral Surg Oral Med Oral Pathol** **53**:441–449, 1982
 19. Raftery AT: Absorbable haemostatic materials and intraperitoneal adhesion formation. **Br J Surg** **67**:57–58, 1980
 20. Rybock JD, Long DM: Use of microfibrillar collagen as a topical hemostatic agent in brain tissue. **J Neurosurg** **46**:501–505, 1977
 21. Silverstein ME, Keown K, Owen JA, et al: Collagen fibers as a fleece hemostatic agent. **J Trauma** **20**:688–694, 1980
 22. Spiller M, Tenner MS, Couldwell W: The effect of absorbable hemostatic agents on $1/T_1$ of blood: an in vitro relaxometry study with implications for postoperative MRI. **Proc Intl Soc Magn Reson Med** **8**:414, 2000 (Abstract)
 23. Wagner WR, Pachence JM, Ristich J, et al: Comparative in vitro analysis of topical hemostatic agents. **J Surg Res** **66**:100–108, 1996
 24. Wahlstrom E, Yadegar J, Amodeo P, et al: Comparative tissue reactivity to topical hemostatic agents in the periureteral area. **Arch Surg** **118**:1375–1377, 1983
 25. Zoucas E, Goransson G, Bengmark S: Comparative evaluation of local hemostatic agents in experimental liver trauma: a study in the rat. **J Surg Res** **37**:145–150, 1984

Manuscript received December 20, 2000.

Accepted in final form June 26, 2001.

This work was supported by a grant from Mallinckrodt, Inc. to Dr. Tenner, and by Grant No. NS01672 from the National Institute of Neurological Disorders and Stroke to Dr. Couldwell.

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