

Necrotizing effect of phenol on normal tissues and on tumors

A study on postoperative and cadaver specimens

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We investigated the necrotizing effect of a 75% alcoholic solution of phenol on normal tissue harvested during surgery (muscles, fatty or connective tissue) or post mortem (peripheral nerves, arteries, epidermal tissue, joint and epiphyseal cartilage) and on tumor tissue (60 samples freshly harvested from patients suffering from bone tumors). The necrotizing effect was measured by determining the thickness of the cell layers demonstrating nuclear pyknosis or necrosis after 2 min of phenolization in a light microscope by ocular measurements in μm .

No effect could be seen in epidermal tissue and in cartilage, whereas all other normal tissues exhibited necrotic zones between 40 and 500 μm . In all the tumors except those with chondromatous tissue, necrotic zones between 40 and 1000 μm were found. No difference in extension of the necrotic zone was seen between specimens from benign and malignant tumors and tumor-simulating processes. Phenolization cannot be recommended for the treatment of chondromatous tumors.

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Phenol has been used to avoid recurrences of intralesionally resected benign bone tumors (Bloodgood 1910, Dahlin and Ivins 1972, Capanna et al. 1985). In our preliminary investigations the maximal devitalizing effect was achieved by using a 75% alcoholic solution of phenol; we investigated the necrotizing effect of this solution on tumorous and nontumorous tissues.

Material and methods

10 nontumorous samples, 10 × 10 mm in size, each from muscles, fatty tissue and connective tissue, were harvested in bone tumor operations, and 4 samples each of vessels, peripheral nerves, epidermal and cartilage tissues were harvested from fresh cadavers on an average of 6 hours post mortem. The material from fresh cadavers demonstrated no signs of autolysis histologically and the cells could be seen very well in the histologic slides; we therefore consider the use of a fresh cadaver as acceptable. Moreover, 60 freshly harvested preparations of bone tumors or tumor-simulating processes of the same size were investigated.

Immediately after harvesting, the specimens were treated for 2 min in a 75% alcoholic solution of phe-

nol (75% phenol in 20% ethanol representing the least possible alcohol concentration); thereafter, neutralization was performed for 10 min using 8.4% sodium bicarbonate (according to Lang et al. 1991). After extensive washing with physiological saline, fixation was performed using 8% neutralized formalin. Specimens containing bone were imbedded in methyl methacrylate without prior decalcification, cut into three slices 2 μm thick and stained with Giemsa.

Specimens without bone were imbedded in paraffin, and staining was performed using hematoxylin-eosin. As controls, similar sections of the same specimens were treated in exactly the same way, without application of phenol.

As it was soon found that chondromatous tumors did not react to phenol treatment, specimens from 3 patients suffering from this type of tumor (Table 1, position, 11, 13, 41) were treated for 10 min with 2 mL chymopapain (3.0 nkat corresponding to 2000 U/mL chymodiactin®) and subsequently treated with phenol, as described above.

Specimens were evaluated macroscopically with respect to the change in color; the histological-qualitative assessment of the necrosis was performed by distinguishing between devitalized areas with predominant total necrosis of cells and areas exhibiting

Table 1. Mean thickness (μm) of the necrosis zone in the different bone tumors

Tumor	Necrosis zone
Metastasis	410
Sarcoma	343
Chordoma	520
Giant cell tumor	462
Unicameral bone cyst	448
Aneurysmatic bone cyst	446
Intraosseous ganglion	286
Nonossifying fibroma	180

pyknotic nuclei or nuclear shadows, respectively. Furthermore, minimal and maximal extension of necrosis was measured by an ocular eyepiece (in μm) and mean values were determined.

Statistical comparison was performed using extension and degree of necrosis, distinguishing between predominant nuclear pyknosis, total necrosis of nuclei and mixed forms within muscles, fatty tissue and connective tissue, on the one hand, and within bone cysts, benign and malignant bone tumors, on the other hand (Fisher PLSD, Scheffe F-test).

Results (Table 1)

Histological evaluation of normal tissue

Muscles. A mean zone of necrosis of 290 (180–380) μm could be detected. All preparations exhibited nuclear shadows as well as total necrosis.

Fatty tissue. The mean necrotic zone was 200 (120–160) μm and all nuclei exhibited total necrosis.

Connective tissue. The effect of phenol treatment was most extensive within the connective tissue exhibiting an average necrosis zone of 340 (200–500) μm . Total necrosis of all the cell nuclei was observed in all cases but one.

Vessels (arteries). The effect of phenol treatment was minimal in the adventitia (40–80 μm); in the intima, a necrotic effect could be observed in only a single case. No other preparations exhibited necrosis of the intima.

Peripheral nerves. The necrotizing effect of phenol treatment on nerves was limited (average 160 μm) and the sections exhibited pyknoses and total necroses in some areas.

Epidermal tissue. No histological effect of phenol treatment was observed.

Cartilage. Phenol treatment had no effect on the joint and epiphyseal cartilage.

Comparison of necrosis zones induced by phenol treatment in muscle, fatty tissue and connective tissue revealed larger zones of necrosis in muscle and connective tissue than in fatty tissue ($P < 0.05$); moreover, differences between fatty and connective tissue and muscles were found with respect to the type of necrosis of nuclei with more cases of total necrosis in fatty and connective tissue than in muscles, $P < 0.05$.

Histological evaluation of tumors

Chondromatous tumors (3 chondrosarcomas, 13 chondromas, 1 chondromyxoma fibroma, 1 chondroblastoma). In no case could any effect of phenol treatment be detected. Preincubation with chymopain resulted in dimming of the fluid; however, necrosis was not found in the histological preparation.

Giant cell tumors (n 9). In all cases, application of 75% phenol resulted in necrosis of the superficial cell layers. Extension of necrosis was rather uniform (range 320–600 μm ; mean 470 μm). When giant cells were present on the surface, these giant cells also underwent necrosis. Within such tumors, total necrosis mainly was usually detected in the superficial cell layers (Figure 1).

Bone cysts (6 unicameral, 3 aneurysmal). In all cases of juvenile and aneurysmal cysts, phenol treatment resulted in zones of necrosis between 140 μm and 800 μm . Within this group, necroses with complete destruction of the nucleus as well as necroses containing pyknotic nuclei or nuclear shadows occurred.

Intraosseous ganglia (n 3). The preparations exhibited a relatively narrow zone of necrosis (mean 290 μm) partly with nuclear shadows, partly with total necroses.

Non-ossifying fibromas (n 2). The effect of phenol treatment was minimal (necrosis 60 μm ; nuclear shadows).

Chordoma (n 1). Phenol treatment caused necroses (mean 520 μm ; total destruction of cellular nuclei).

Metastases (4 unknown primary, 3 breast, 2 renal, 1 prostatic). In this group, a relatively wide range of thickness of the necrotic zone (100–1000 μm) was observed (mean 410 μm) which showed predominantly devitalized zones with persistent nuclear shadows (Figure 2).

Plasmocytoma (n 1). Wide zones of necrosis (560 μm) and nuclear shadows.

Sarcomas (excluding chondrosarcomas) (1 MFH, 1 clear cell, 1 angiosarcoma, 1 postirradiation, 1 osteosarcoma). Relatively small zones of necrosis

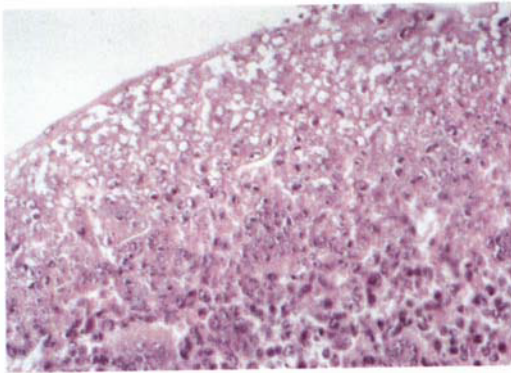


Figure 1. Giant cell tumor, treated with 75% phenol; pyknosis of nuclei in superficial cell layers, also involving giant cells; below vital tumor tissue (HE, $\times 400$).

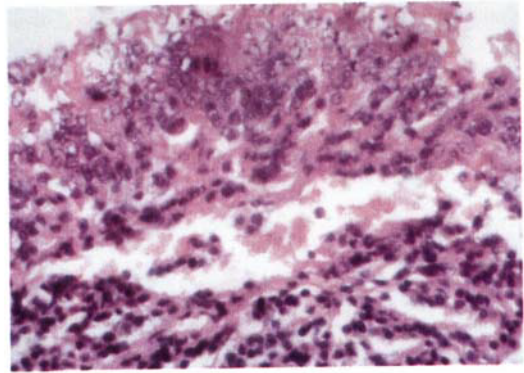


Figure 2. Bone metastasis from breast carcinoma, treated with 75% phenol; partial complete necrosis, partial pyknosis of nuclei; below increasing number of vital tumorous nuclei (HE, $\times 400$).

could be observed (range 200–600 μm), in which total necroses predominated.

With the exception of the cartilagenous tumors, all other tumors showed zones of necrosis of varying width. Some superficial cell layers exhibited total necroses without detectable remnants of cellular nuclei, others exhibited necroses with pyknotic cellular nuclei still visible or with nuclear remnants.

No significant difference could be detected within the 3 groups (cysts, benign diseases, malignant tumors) regarding the extension of the necrotic zones. The percentage of total necrosis was significantly higher in the group of benign tumors than in the groups of cysts and malignant tumors ($P < 0.05$).

Discussion

Local phenol treatment during surgery has been reported to prevent recurrences of benign bone tumors and juvenile and aneurysmal bone cysts (Campanacci et al. 1986, Schiller et al. 1989), giant cell tumors (Capanna et al. 1985, 1990, Eckart and Grogan 1986, Rock 1990, Szendroi 1992) and chondroblastomas (Dahlin and Ivins 1972). To our knowledge, no studies have been performed concerning the necrotizing effect of phenol treatment.

Previously we found that a solution of phenol in 75% alcohol had the most pronounced necrotizing effect on bone marrow cells (Lang et al. 1991). Phenol is a weak acid that affects denaturation in tissues having a high protein concentration without coagulation (Rock 1990). This is probably the reason for differences in the effects of 75% phenol solution on

various body tissues. We could not confirm the occurrence of necroses in human epidermal tissue after the local application of phenol, as reported by Abraham (1972).

Phenol seems to induce various degrees of extension of necrosis zones within different tissues. However, no differences could be determined regarding its efficacy different tumor types. We assume that the necrotizing effect of the phenol solution may be dependent on the tissue involved and on its cell count, regardless of the type of tumor.

In no case did phenol have any apparent effect on cartilagenous tissue and cartilagenous tumors. This finding is in contrast to clinical results reported by Capanna et al. (1985), who found a decreased rate of local recurrences when chondroblastomas were treated with phenol. Because there is no proof of an effect of phenol solution on chondroic material, phenol should not be used in surgery for chondromas, chondromyxoid fibromas, chondroblastomas or low-grade chondrosarcomas.

The application of an alcoholic solution of 75% phenol to tumors and tumor-simulating lesions of non-cartilagenous tissues causes only a thin layer of necrosis. Therefore, thorough mechanical removal of the tumor tissue is mandatory even when treatment with phenol solution is used.

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