# Prolongation of epidural bupivacaine analgesia with glycerin

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*Glycerin has been used as a drug carrier/depot, but never with local anaesthestics. This study was an attempt to use the slow drug release mechanism to prolong the anaesthetic effects of bupivacaine in epidural block. Twenty-seven adults with cancer pain were prospectively selected according to their primary lesions and problems, but their allocation to study groups was randomized. Group I (n = 13), received 5 ml bupivacaine, 0.125% in normal saline via a previous implanted epidural catheter. When the pain returned to its original intensity, the same amount of the same strength anaesthetic dissolved in 50% glycerin was given via the same catheter. Group II (n = 14) received the same solutions, but in the reverse order. Also five patients in each group received plain 50% glycerin prior to administration of the anaesthetic solutions to serve as controls. The pharmacological effects were assessed by the blinded observers. Analgesia produced with glycerin solution was prolonged compared with the saline solution (12.2 vs 7.2 and 11.6 vs 7.4 hr, $P < 0.01$). The order of giving the solution did not produce any differences. Plan 50% glycerin did not produce analgesic effects. Neither motor blockade nor other adverse effects or complications were observed in either group. It was concluded that 0.125% bupivacaine in 50% glycerin administered epidurally is not neurotoxic. The prolongation of analgesia observed is attributed to the slow release of bupivacaine from the glycerin base which functions as drug depot. In addition to relief of chronic pain, this novel approach may have other clinical applications such as the relief of labour or postoperative pain.*

*La glycérine sert de vecteur et de réservoir à bien des substances médicamenteuses mais on ne l'a jamais utilisée avec des anesthésiques locaux. Cette étude veut tirer profit du mécanisme de libération retardée pour prolonger les effets de la bupivacaïne pendant le bloc épidural. Vingt-sept adultes souffrant de douleur cancéreuse font partie de cette étude randomisée et prospective. Ils sont distribués en trois groupes. Le groupe I (n = 13) reçoit bupivacaïne 0,125% dans le soluté physiologique 5 ml par un cathéter préalablement implanté. Lorsque la douleur revient à son intensité initiale, on injecte par le cathéter épidural la même quantité et la même concentration de l'anesthésique dissout dans la glycérine 50%. Le groupe II reçoit les mêmes solutions, mais dans l'ordre inverse. Cinq patients de chaque groupe reçoivent seulement de la glycérine 50% par la même voie avant l'administration de l'anesthésique et servent ainsi de contrôles. Les effets sont évalués par un observateur neutre. L'analgésie produite par la solution glycérinée dure plus longtemps que la solution préparée avec le soluté physiologique (12,2 vs 7,2 et 11,6 vs 7,4 $P < 0,01$). L'ordre de l'administration n'a pas d'importance. La glycérine 50% seule n'a pas d'activité analgésique. On n'a pas observé de bloc moteur ni d'effets défavorables dans aucun des groupes. On en conclut que la bupivacaïne 0,125% dans la glycérine 50% ne cause pas de neurotoxicité en administration épidurale. La prolongation de l'effet est attribuée au fait que la glycérine, qui agit comme un réservoir, libère lentement son contenu de bupivacaïne. En plus de son efficacité contre la douleur chronique, on peut entrevoir pour cette modalité thérapeutique de nouvelles applications comme le soulagement de la douleur obstétricale et postopératoire.*

**Key words**
ANAESTHETICS: local, bupivacaine;
PAIN: chronic.

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Glycerin has long been used with phenol as a drug carrier/depot for control of late-stage intractable pain for cancer patients.[1] However, to our knowledge, glycerin has never been used in conjunction with a local anaesthetic agent to prolong its pharmacological effects. Our study is an attempt to use this slow drug release mechanism to extend further the analgesic effects of a popular long-acting local anaesthetic agent, bupivacaine, in a commonly used technique, epidural block.

## Methods

Following institutional Human Investigation Committee approval and patient informed consent, 15 adult patients at Zhong-Shan Hospital in Shanghai, and 12 adult patients at China Medical Center in Taipei, China were enrolled into this study for relief of cancer pain. Patients were selected prospectively according to their primary lesions and problems, but their allocation to the study groups was random. Patients who were receiving other active pain treatment, whether employing a pharmacological or non-pharmacological approach, or those with altered mentalities were excluded. Patients in Group I ($n = 13$) received 5 ml bupivacaine, 0.125% in normal saline via a previously implanted epidural catheter. Injections were followed by irrigation of the catheter with 0.2 ml saline (the dead space of the catheter was previously evaluated and never exceeded 0.16 ml). Later, when the pain returned to its original intensity, the same amount of the same strength anaesthetic dissolved in 50% glycerin was administered via the same catheter. Patients in Group II ($n = 14$) also received both aqueous and glycerol solutions, but in reverse order. All patients were in supine position during and for 30 min following injections. Five patients in each group received plain 50% glycerin one day prior to the administration of anaesthetic solution to serve as a control. The pharmacological effects were assessed every minute for 30 min, and thereafter, every 30 min by evaluation of the intensity and duration of sensory and motor blockade employing visual analogue scale[2,3] and modified Bromage scale.[4] The observers as well as the patients were blinded to the solutions given. Patients' vital signs were closely monitored during the study. Results obtained were analyzed by Student's t test. A $P$ value $< 0.05$ was considered to be significant.

## Results

The two groups were demographically compatible; patients did not differ with regard to sex, age, weight and height (Table I). The sites of their primary lesions and epidural catheter placement are shown in Table II. Both groups were also compatible in this regard. The mean times of onset for the saline and glycerol solutions were 8.8 ± 1.3 min vs 9.2 ± 1.1 min and 9.4 ± 1.8 min vs 9.9 ± 1.4 min, respectively for Group I and Group II (NS). The median spread of anaesthetic was 5.4 and 5.1 segments for the saline solution and 5.3 and 5.2 segments for the glycerol solution (NS). The mean durations of analgesia were 7.2 ± 1.6 and 7.4 ± 1.2 hr for the saline solutions, and 12.2 ± 1.6 and 11.6 ± 1.7 for the glycerol solutions respectively ($P < 0.01$) regardless of the sequence of drug administration (Table III). The quality of analgesia produced by saline solution and glycerol solution was similar (NS). Most patients in both groups obtained satisfactory pain relief (VAS < 5). No clinical signs of nerve block were detected after plain glycerin solution. Neither motor blockade nor any adverse reactions were observed in either group. Vital signs were stable in both groups. Three patients' arterial blood pressure decreased more than 20 mmHg but less than one-third of their base line readings. They all responded promptly to fluid infusion or a small dose (5 mg) of ephedrine.

TABLE I Patient characteristics

| | *Group I (n = 13)* | *Group II (n = 14)* |
|---|---|---|
| Sex (M/F) | 8/5 | 9/5 |
| Age (yr.)* | 66 ± 6.6 | 68 ± 4.3 |
| Height (cm)* | 165 ± 2.2 | 167 ± 1.6 |
| Weight (kg)* | 62 ± 4.3 | 65 ± 3.7 |

*Mean ± SD.

TABLE II Sites of primary lesion and epidural catheter

| *Sites* | | | |
|---|---|---|---|
| *Lesion* | *Catheter* | *Group I (n = 13)* | *Group II (n = 14)* |
| Bladder | $L_{4-5}$ | 2 | 1 |
| Breast | $T_{6-7}$ | 2 | 2 |
| Liver | $T_{9-10}$ | 2 | 2 |
| Lung | $T_{7-8}$ | 2 | 2 |
| Pancreas | $T_{9-10}$ | 0 | 1 |
| Prostate | $L_{4-5}$ | 0 | 1 |
| Rectum | $L_{4-5}$ | 5 | 4 |
| Testis | $L_{4-5}$ | 0 | 1 |

TABLE III Pharmacological effects

| | *Group I* | | *Group II* | |
|---|---|---|---|---|
| | *Saline* | *Glycerin* | *Glycerin* | *Saline* |
| Analgesia | | | | |
| - Onset (min)*[1] | 8.8 ± 1.3 | 9.2 ± 1.1 | 9.9 ± 1.4 | 9.4 ± 1.8 |
| - Duration (hr)*[2] | 7.2 ± 1.6 | 12.2 ± 1.6 | 11.6 ± 1.7 | 7.4 ± 1.2 |
| Spread (segments)†[1] | 5.4 | 5.3 | 5.2 | 5.1 |
| Quality (VAS)[1] | | | | |
| - 0–1 | 10 | 11 | 11 | 10 |
| - 2–3 | 2 | 1 | 2 | 2 |
| - 4–5 | 1 | 1 | 1 | 2 |
| - 6–10 | 0 | 0 | 0 | 0 |
| Motor blockade | 0 | 0 | 0 | 0 |

*Mean ± SD; † = Median.

[1] Not significant between agents or groups.

[2] Statistical significant between agents ($P < 0.01$); not significant between groups.

## Discussion

Glycerin is a naturally occurring trihydric alcohol with a high viscosity and osmolarity. It is miscible with water and alcohol and has been used as a vehicle or stabilizer for drugs.[5] Glycerin absorbs water and, therefore, in high concentrations, is somewhat dehydrating and irritating to exposed tissues.[5] The 50% glycerin with bupivacaine solution we used has a pH value of 6.0. Glycerin is part of the neutral fat (triglyceride) molecule and thus a normal metabolic intermediate in animals and human beings. It is known that glycerol is converted by liver to glycogen and other carbohydrates.[6] Glycerin has been given orally (50 or 75%) or intravenously (10%) to reduce intracranial or intraocular pressure.[5,7,8] It also may be applied topically to reduce corneal oedema. Local injection of glycerin with or without teflon has long been used for various purposes in otolaryngology.[9-12] In anaesthesia, the use of glycerin and phenol for the control of intractable cancer pain was popularized by Maher,[1] who, in 1955, described the subarachnoid administration of phenol in glycerin to produce a chemical rhizotomy. Furthermore, pain relief from trigeminal neuralgia by selective destruction of the pain-bearing nerve fibres has been achieved by the instillation of glycerin among the trigeminal rootlets (percutaneous retrogasserian glycerol rhizolysis).[13]

In this study, we used 50% glycerin solution because it is a physiologically occurring substance and therefore likely to be safe and harmless. It is a markedly diluted solution thus easy to inject through an elongated epidural catheter and will not irritate the exposed tissues or cause any complications by inadvertent intravascular injection.[5-9] The observed prolongation of analgesia was attributed to the slow release of the local anaesthetic agent from the glycerin base which functions as a drug depot, that ensures the availability of an effective drug concentration within the epidural space. Langerman *et al.* employed the same slow release mechanism and reported the use of lipid (iophendylate) solution for prolongation of spinal anaesthesia[14] as well as epidural anaesthesia.[15] Mashima *et al.*[16] used liposome for the same purpose. It appears that this controlled-release formulation concept has been grasped all over the world.

As concentrated glycerin possesses a neurolytic effect,[13] the prolongation of analgesia could have been due to neurotoxicity. This is very unlikely, as the pain relief obtained was only temporary and we have not observed any neurological sequelae in any of our patients. Nonetheless, this possibility deserves further investigation. We therefore have included five patients in each group, who were given plain glycerin prior to the anaesthetic solutions, during the latter part of the study. However, at the time this manuscript was prepared, all our patients are alive, and we thus have not done any histopathological studies.

The current approach to the relief of chronic pain involves either modification of efferent nociceptive impulses or alternation of the central interpretation of those impulses. Nevertheless, when an organic cause exists, nerve blockade generally plays a major role in pain management.

Despite its popularity, continuous epidural anaesthesia, either by infusion or by intermittent doses, is technically complicated, time-consuming and expensive. Furthermore, it may cause neurological toxicity or other complications.[17,18] Thus, it would be advantageous if this slow drug release formulation could replace the continuous technique in certain clinical situations.

In conclusion, epidural administration of bupivacaine in glycerin prolongs its analgesic effects. The slow drug release formulation, in addition to relief of chronic pain, may also have other clinical applications, such as the relief of labour pain or postoperative pain. If the quality of analgesia is sufficient, it may well be useful for surgical anaesthesia. This slow drug release formulation approach is worthy of further investigation.

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