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Leukocytosis after fluid loading and induction of epidural anesthesia

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Abstract: The present study shows that leukocytosis occurs from fluid loading and from the small amounts of adrenaline given epidurally. Five healthy volunteers received an intravenous infusion of 25 ml·kg^{-1} b.w. of Ringer's acetate solution over 15, 30, 45, and 80 min, and epidural anesthesia (EDA) was induced in 25 urology patients using mepivacaine 2% with or without adrenaline 1:200 000. In the volunteers, we found that the total leukocyte count increased by up to 33% within 1 h after rapid volume loading. This increase was accounted for by neutrophils and lymphocytes. In the patients, the leukocyte count increased by 32% during the onset of EDA when mepivacaine with adrenaline was used. This increase was accounted for by lymphocytes. Our results suggest that caution is needed when interpreting the importance of a raised leukocyte count in samples taken in association with fluid loading and also when EDA is induced by a local anesthestic solution that contains adrenaline.

Key words: Adrenaline Epidural anesthesia, Leukocytes, Lymphocytes, Fluid therapy, Adverse effects

Introduction

In recent years, there has been an increasing interest in the effects of anesthesia and surgery on the immune system. A marked change in the number of leukocytes in peripheral blood and the responsiveness of these cells in certain in vitro tests are factors often thought to indicate an alteration in the resistance of the body to infection [1,2]. However, the effects of fluid therapy and anesthesia on leukocytes are difficult to study, as both the surgical procedure and hemorrhage interact with them [3,4].

The aim of the present study was to look for a possible effect of fluid loading and induction of lumbar epidural anesthesia (EDA) on the total leukocyte count and the distribution of leukocyte cell types in peripheral blood. Measurements were performed in urology patients but, for safety reasons, the effect of more vigorous fluid loading was studied in younger volunteers. We used local anesthetic solutions both with and without adrenaline, as many studies show that this hormone alone produces a redistribution of white cells between peripheral blood and the lymphatic system [5–7].

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Materials and methods

The study consists of two parts: an experimental study and a clinical study. Ethics Committee approval was obtained and patients and volunteers gave their informed consent to participate.

Experimental study

Five healthy female hospital workers (mean age 32, range 25–40) volunteered to be given an intravenous infusion of 25 ml·kg^{-1} b.w. of an isotonic glucose-free crystalloid solution, Ringer's acetate, on four different occasions. After an overnight fast, the infusions were begun between 8 a.m. and 10 a.m. and were administered at a constant rate over periods of 15, 30, 45, and 80 min by infusion pumps.

Clinical study

Twenty-five male patients (ASA physical status I–II, mean age 71, range 38–85) were studied during the induction of EDA prior to short urological operations. The patients had fasted overnight when given premedication consisting of oxazepam 25–50 mg p.o. (Sobril, Pharmacia, Uppsala, Sweden). During the induction, a fluid load of 15 ml·kg^{-1} b.w. of Ringer's acetate was infused through a venous cannula. The fluid load was administered by infusion pumps at a constant rate over 50 min.

In 19 patients, EDA was induced with 13–16 ml of mepivacaine 2% and adrenaline 1:200 000 (Carbocain-adrenalin, Astra, Södertälje, Sweden). In six patients, EDA was induced with mepivacaine 2% (Carbocain,

Astra). The first 3 ml was always a test dose, and the main dose was given 3 min later. The anesthetic solutions were infused into the epidural space through an indwelling catheter. No vasopressor was given to treat arterial hypotension.

Measurements

Blood samples were drawn from a cannula placed in the cubital vein in the arm not used for infusion. Contamination from dead spaces was ruled out. In the experimental study, the total number of leukocytes in whole blood was measured every 5–10 min during the infusion and every 5–20 min for 2 h after infusion on a Coulter Counter S Plus (Coulter Electronics, Hialeah, FL, USA). The normal range for this analysis is between 3 and 9 $\times$ 10^9 cells·liter^{-1}. Duplicate samples showed a coefficient of variation of 4%. A differential count was also performed by the Coulter Counter before the experiments started, after 50% of the infusion was given, and 40 min after infusion.

In the clinical study, the number of leukocytes in whole blood was measured on 13 occasions: (1) before any fluid was given, (2) after 10 min of fluid loading, (3) after 20 min, just before the local anesthetic was injected, and thereafter (4) every 3 min for 30 min. At the end of this period, analgesia level was determined by the pin-prick test and adequate surgical analgesia was confirmed. A differential leukocyte count was obtained before any fluid was given and 20 min after the local anesthetic solution had been given. The arterial systolic pressure was measured with a sphygmomanometer when blood samples were drawn.

Data are expressed as the mean and standard error of the mean (SEM). One-way analysis of variance (ANOVA), simple linear regression analysis, and the paired *t*-test were used for statistical evaluations.

Results

Experimental study

The women who were subjected to fluid loading with Ringer's acetate showed a decrease in the total leukocyte count during infusion. Serial measurement of the blood hemoglobin concentration showed the same trend. The decrease was seen in all leukocyte subtypes. Later, there was an increase in leukocyte count, and this was fully developed 45 min after each infusion was completed. At that time, the number of leukocytes in the peripheral blood had increased by 19% (paired *t*-test, $P < 0.001$), but, for the highest infusion rate, the average increase amounted to 33% (Fig. 1). The differential count showed that the neutrophils and the lymphocytes were equally responsible for the leukocytosis.

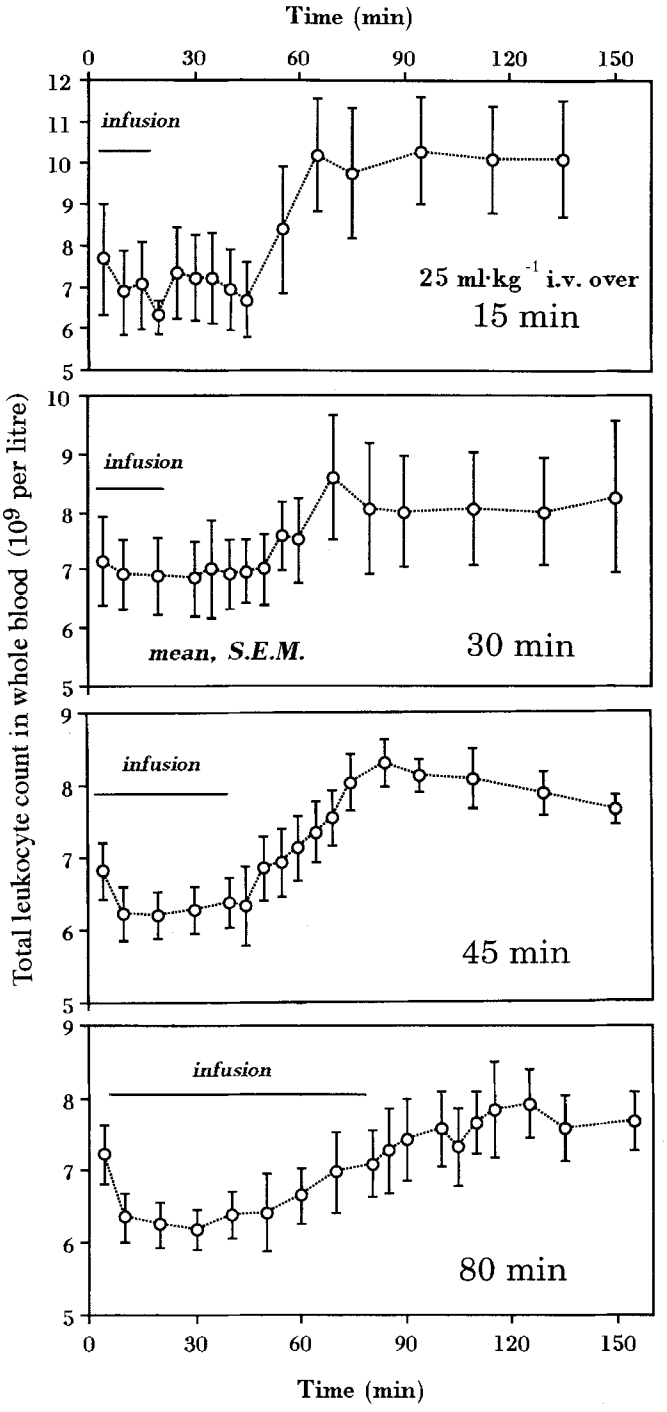

Fig. 1. The blood leukocyte count before, during, and after intravenous infusion of 25 ml·kg^{-1} of Ringer's acetate solution over 15, 30, 45, and 80 min in 5 female volunteers

Clinical study

A marked elevation of the leukocyte count occurred when EDA was induced with mepivacaine containing adrenaline (Fig. 2). The peak occurred 15 min after injection of the main dose of anesthetic (18 min after the test dose) and amounted to 32 $\pm$ 5% above the baseline

Table 1. Differential leukocyte count before fluid loading and 20 min after induction of EDA

	Mepivacaine 2% with adrenaline (n = 12)[a]		Mepivacaine 2% (n = 6)	
	Before volume loading	20 min after induction of EDA	Before volume loading	20 min after induction of EDA
Leukocytes (total)[b]	7.18 ± 0.40	9.58 ± 0.44*	7.00 ± 0.84	6.58 ± 0.73
Neutrophils	4.20 ± 0.35	4.66 ± 0.53	4.37 ± 0.71	4.15 ± 0.68
Lymphocytes	2.25 ± 0.18	3.59 ± 0.35*	2.08 ± 0.32	1.80 ± 0.30
Monocytes	0.57 ± 0.10	0.62 ± 0.08	0.38 ± 0.03	0.34 ± 0.03
Eosinophils	0.13 ± 0.02	0.13 ± 0.03	0.20 ± 0.06	0.15 ± 0.04
Basophils	0.02 ± 0.01	0.05 ± 0.02	0.05 ± 0.02	0.03 ± 0.02

Changes were evaluated by the paired t-test.
* $P < 0.001$.
[a] Differential count was not obtained in the first 7 cases.
[b] Unit = 10^9 cells/l.

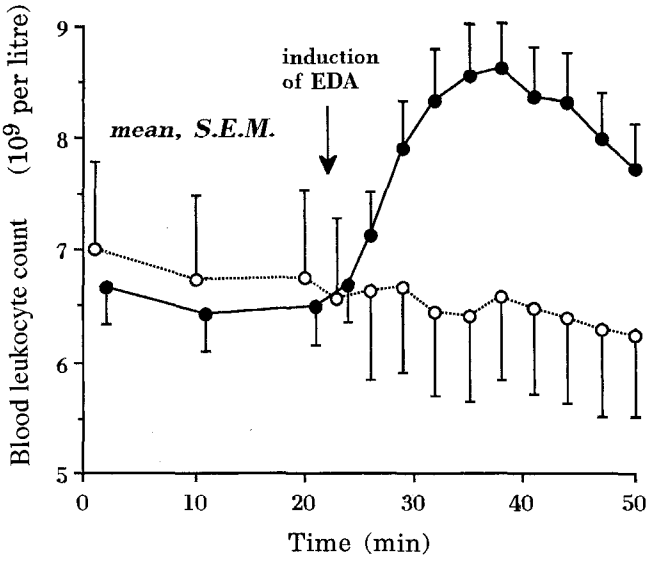

Fig. 2. The blood leukocyte count before, during, and after induction of epidural anesthesia (*EDA*) in 25 urology patients, using mepivacaine 2% (*open circles*) and mepivacaine with adrenaline 1:200 000 (*closed circles*)

($P < 0.001$). At this time, nine patients (47%) had a leukocyte count above the normal range, while only one (5%) had leukocytosis before EDA was induced. The differential count showed that the elevation of the leukocyte count was due to lymphocytosis. In contrast, the patients in whom EDA was induced with mepivacaine 2% showed no elevation of the leukocyte count and no changes in the differential count (Table 1).

There was no difference in the extent of analgesia (upper level 5.7 ± 0.6 Th) or the degree of blood pressure reaction to the blockade (decrease in systolic arterial pressure to 75 ± 4% of the baseline) between the patient groups that received mepivacaine with and without adrenaline (ANOVA). In addition, linear regression analysis revealed no correlation between these variables and the leukocyte count.

Discussion

Our results show that fluid loading and induction of EDA have effects on the leukocyte count. In the volunteer experiment, a slight lowering of the number of leukocytes in the blood occurred during infusions of crystalloid solution, an effect that was probably caused by dilution. However, from 30 min after the infusion and onwards, we observed a marked increase in the leukocyte count. This appears to be a specific effect of the fluid load. The leukocytosis was consistent and occurred regardless of how fast the crystalloid solution was infused, although a more pronounced change was seen after the most rapid infusions. Interestingly, the leukocyte count showed little tendency to return to normal levels during the period of study, even though the follow-up time after infusion was as long as 2 h.

The clinical part of the study demonstrates that the leukocyte count rises when EDA is induced with mepivacaine containing adrenaline. A slight dilutional decrease in the leukocyte count occurred also during this fluid loading, whereupon an injection of mepivacaine containing adrenaline boosted a rapid increase in the blood leukocyte count. The fact that no change in the number of leukocytes was seen after induction of EDA with mepivacaine alone, despite similar blood pressure responses and extents of analgesia, strongly suggests that the leukocytosis was caused by systemic absorption of adrenaline from the epidural space. Further evidence of adrenaline being the cause of the leukocytosis is seen from the distribution of white cell types in the peripheral blood. We found primarily

an increase in the number of circulating lymphocytes, which is a known effect of adrenaline [5–9].

Crystalloid solutions have been assumed not to have any effect on the distribution of leukocytes in the body. Previous studies have probably overlooked this fact because samples were not taken at appropriate times. However, the present results show that fluid loading must be regarded as a factor to be taken account of in studies of leukocyte distribution and the immune response during anesthesia and surgery. The mechanism of the leukocytosis we observed is not clear. The distribution of leukocyte subgroups showed a change different from that seen after the epidural administration of adrenaline. We hypothesize that the new cells were recruited from the interstitial space. When Ringer's solution has become distributed over the entire extravascular space, most of the fluid must travel back from the interstital space to the bloodstream again to reach the kidneys before it can be excreted. As more than half of the leukocytes in the body are found in the interstitial space, a number of them are probably transported back to the bloodstream along with the bulk flow of fluid. However, the present result can also be explained by changes in the intravascular distribution of white cells.

We were surprised to find that the fairly small dose of adrenaline used as an adjuvant during induction of EDA (about 0.05 mg) was enough to cause leukocytosis. Higher doses have been used in the experimental studies of leukocytosis from adrenaline [6–9]. The prompt effect can be explained, in part, by the effective absorption of adrenaline from the epidural space. For example, the plasma level of adrenaline triples in response to EDA induced with the same amount of mepivacaine with adrenaline as in the present study [10] while a fourfold higher dose is required to obtain the same increase if adrenaline is given by subcutaneous injection [6].

The two situations with an increased leukocyte count that we describe are important cornerstones in the practice of any anesthetist. The results show that caution is needed when interpreting the importance of a raised leukocyte count in association with fluid loading and EDA. For example, the APACHE score might be falsely high if rapid fluid loading is performed before the leukocyte count is measured, or if the patient is treated with continuous EDA using a local anesthetic that contains adrenaline.

Our findings may also be of some significance to the immune response, although this is, at present, very speculative. The raised leukocyte count is probably evidence of increased recirculation of leukocytes, in particular of lymphocytes. This would increase the chances of contact between an aggressor and the immune cells and, in theory, promote a more prompt immune response. The magnitude of the increase in the leukocyte count also suggests that the adrenaline absorption after induction of EDA has qualitative effects on the leukocytes. Most studies show an increase in natural killer cell activity in response to adrenaline [6,7,9] although some other immune functions that can be studied in vitro may become transiently inhibited [8]. The duration of these effects is about 2 h [6] although some of them may last as long as 24 h [7].

In conclusion, we have demonstrated that both fluid loading alone and adrenaline absorption during the induction of EDA result in an increase in the number of leukocytes in whole blood.

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