SCENAR-Therapy Effects on Blood Pressure and State of the Blood Plasma Oxidant-Antioxidant System in Patients with Compression Injuries Complicated by Acute Renal Failure

Summary:
The effect of SCENAR-therapy on the clinical course of acute renal failure, lipid peroxidation and arterial pressure parameters in patients with compression injuries has been studied. It has been proven that SCENAR-therapy combined with sublingual intake of 2.5 mg Isradipine twice a day is the most effective method for correcting the arterial pressure in patients with acute renal failure. Using the SCENAR-therapy eliminates the effect of increased level of nitrosohemoglobin fractions against a background of Isradipine and practically relieves oxidative stress in the patient’s blood plasma.

Key words: SCENAR-therapy, compression injury, acute renal failure, arterial hypertension, lipid peroxidation.

Compression injury is one of the severest forms of soft tissue injuries and in most cases it is complicated by myoglobinuric nephrosis and oligoanuric acute renal failure (ARF). The death rate in oligoanuric ARF is pretty high (50 to 70%), and when followed by multiple organ failure, it can reach up to 85-95%. In survivors, the chronization of the process followed by regular hemodialysis is possible in only 1-3% cases [12]. The background for development of nephrosclerosis and patient disablement is the severity of kidney failure as well as complications in many organs and systems including arterial hypertension syndrome. The syndrome is characterized by persistent course, resistance...
to intensive ARF therapy, antihypertensive therapy, including ACE inhibitors\(^1\). In this pathology, high arterial blood pressure may be caused by several factors, and oxidative stress is of no little significance here [10, 11]. All that provides background for optimizing treatments for such patients, including the correction of arterial hypertension and influencing the state of the prooxidant-antioxidant system, and makes this problem current.

Besides good hypotensive effect, the reason why we chose dihydropyridine calcium antagonists of second generation was the evidence that this group of preparations is capable to improve the tissue anoxia tolerance and increase the antioxidant effect under oxidative stress [3, 15, 19, 21]. And Isradipine was selected because of its ability to increase the glomerular filtration rate and renal blood flow [1, 16], which is important for ARF patients.

Results of the research and investigations which discovered the capability of transdermal neuroadaptive regulation to non-specifically reduce the oxidative stress in patients with early post-infarction angina [9], insomnia [17], bronchial asthma [5] made us consider that including SCENAR therapy in the treatment is reasonable.

The objective of this research was to investigate blood pressure dynamics and state of the lipid peroxidation (LPO) activity and antioxidant system (AOS) of the blood plasma in patients with compression injuries complicated by ARF and arterial hypertension, after using various treatments for correcting the arterial hypertension, including those involving SCENAR therapy.

**MATERIALS AND METHODS**

The patients that had arterial hypertension at the anuric stage of ARF caused by a compression injury were divided into 3 groups. The patients in the control group (n=46) were given standard intensive ARF therapy using extracorporal methods. In the test group I (n=41) the multiple treatment, besides standard therapy, included Isradipine 2.5 mg twice daily sublingually in addition. And in the test group II (n=25) besides standard therapy and Isradipine, the patients received SCENAR-therapy every day. A course of SCENAR-therapy included 8-10 sessions and was finished when diuresis resumed. Considering the tasks and objectives, the patients over 60 were excluded from the investigation.

In SCENAR-therapy two general treatment techniques were used mainly: "3 pathways and 6 points" and "collar zone, forehead, adrenals" [9, 17]. Skin zones were treated with CHANS-SCENAR and no digital techniques were used. Settings: mode **F1**. Stimulation: comfortable (the patient feels slight tingling and vibration); intensive (the patient feels it as almost painful). The energy strength was selected near the zone that was supposed to be treated. If the device stuck somewhere when moving along the routes, it wasn’t taken off the skin but was held down until moving the device downwards became possible. When asymmetries were identified, those areas were treated again until a change in the primary signs (hyperemia, paleness, different sensitivity etc.).

Blood pressure characteristics were registered on admission, on the 1-2 day of diuresis recovery and on transfer to the relevant department. The blood samples for biochemical tests were taken on admission and on the 1-2 day of diuresis recovery.

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\(^1\) inhibitors of Angiotensin-Converting Enzyme
The nitrosohemoglobin level (NOHb) in plasma was measured from the maximum absorption for two wave lengths – 418 and 545 nm using the method by I.I.Stepuro and co-authors (1997). The quantity of conjugated dienes was determined spectrophotometrically using I.D. Stalnaya method (1977). The content of malonic dialdehyde (MDA) was measured by M.D. Stalnaya and T.D. Gorishvili method (1977). To determine Schiff bases, lipids were extracted from plasma using the Bligh-Dyer method (1959). Catalase activity (CA) in the blood plasma was determined using M.A. Korolyuk et al. method (1988). The oxidase activity of ceruloplasmin (CP) was determined using the Revin’s method adapted by V.G.Kolba and V.S.Kamyshnikov (1982).

The control group included healthy people of comparable age (n=20). The data were processed statistically by variance analysis using Student-Fisher T-criterion on a PC IBM Pentium III in the STATISTICA 6.0 application software.

RESULTS AND DISCUSSION

After we analyzed data of all patients with compression injuries complicated by ARF (135 patients), the results were found to be different from those in the literature, according to which hypertension at the onset of ARF (of various genesis) occurs in only 20-30% patients [12], and in oligoanuric ARF, hypertension (if any) is usually low-grade [6]. According to our research, arterial hypertension occurred in 112 patients, i.e. in 83%, which is closer to the data of those researchers who say that in the oligoanuric phase of ARF, hypertension is high-grade in 70 to 72% [4, 7, 18, 20].

The dynamics of blood pressure indices in all 3 groups is provided in Table 1. On admission, systolic pressure (SP) indices (depending on a group) ranged from 140 to 150 mm Hg; diastolic pressure ranged from 80 to 85 mm Hg; average dynamic pressure (ADP) – 101 to 107 mm Hg. All these indices were comparable in all 3 groups.

In the control group, by the time diuresis recovered, pressure indices increased significantly (despite the treatment) as compared to those on admission: SP increased by 8.3%, DP – by 10.0%, ADP – by 9.2%. In test groups by that time there was no significant change in blood pressure indices as compared to the initial ones, except for the significant decrease of SP indices in the test group II. However, almost all indices in these groups (except for DP in the test group I) were significantly lower than those in the control group.

If we compare the hypotensive effect of treatments in test groups I and II, one can notice that in the group that underwent SCENAR-therapy the indices under consideration changed more significantly percentagewise. Thus, while in patients whose treatment included Isradipine SP indices decreased by 2.1%, in the group that was given Iradipine as well as SCENAR-therapy this index (SP) decreased by 7.7%. ADP differences were even more significant. In the test group I, percentagewise DP and ADP increased a little (by 2.7% and 0.6% respectively), and in the test group II – DP and ADP decreased (by 3.1% and 3.7% respectively) as compared with those on admission.
Table 1

Changes in blood pressure indices during the treatment

<table>
<thead>
<tr>
<th>Testing time</th>
<th>Index, mm Hg</th>
<th>SP</th>
<th>DP</th>
<th>ADP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>On admission:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td></td>
<td>143.1±2.9</td>
<td>82.8±1.7</td>
<td>102.9±1.6</td>
</tr>
<tr>
<td>Test group I</td>
<td></td>
<td>148.5±2.3</td>
<td>82.1±1.7</td>
<td>104.2±1.3</td>
</tr>
<tr>
<td>Test group II</td>
<td></td>
<td>146.4±3.1</td>
<td>83.1±1.9</td>
<td>104.5±2.0</td>
</tr>
<tr>
<td></td>
<td>On diuresis recovery:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td></td>
<td>155.0±3.1¹</td>
<td>91.1±3.3¹</td>
<td>112.4±2.9¹</td>
</tr>
<tr>
<td>Test group I</td>
<td></td>
<td>145.4±2.9*</td>
<td>84.3±1.9</td>
<td>104.8±2.0*</td>
</tr>
<tr>
<td>Test group II</td>
<td></td>
<td>135.1±2.6¹*</td>
<td>80.5±2.3*</td>
<td>100.6±2.1*</td>
</tr>
<tr>
<td></td>
<td>On transfer to the relevant department:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td></td>
<td>156.5±2.4¹</td>
<td>89.6±1.5¹</td>
<td>111.9±1.6¹</td>
</tr>
<tr>
<td>Test group I</td>
<td></td>
<td>132.2±2.3¹*</td>
<td>75.2±0.8¹*</td>
<td>94.2±1.2¹*</td>
</tr>
<tr>
<td>Test group II</td>
<td></td>
<td>125.5±2.1¹*</td>
<td>70.5±1.4¹*</td>
<td>80.3±1.5¹*</td>
</tr>
</tbody>
</table>

Note: the second line shows the percentage of the index change as compared with that on admission;
& - P<0.05 as compared with that on admission;
* - P<0.05 as compared with that in the control group;
# - P<0.05 as compared with that in the test group I.

Control group patients, irrespective of recovered diuresis and their general improvement, have been transferred for aftertreatment to the Multiple Injury Department with high blood pressure indices that were even higher than those on admission (SP – by 9.4%, DP – by 8.2%, ADP – by 8.7%). In test group I patients only SP remained a little higher (132.2±2.3 mm Hg), and in test group II patients central hemodynamics indices became normal.

Table 2 shows the indices of free-radical lipid peroxidation (LPO) and antioxidant system (AOS) activity of the blood plasma in all 3 groups on admission.

From the table one can see that on admission in all patients with compression injury and full-scaled clinical picture of acute renal failure with hypertensive syndrome both fractions of nitrosohemoglobin tended to increase. The increase of NOHb (418 nm) level in the groups ranged from 10.2% to 24.8%, increase of the NOHb (545 nm) level – ranged from 16.5% to 27.7%.
Table 2
Indices of LPO and AOS activity of the blood plasma in all 3 groups on admission

<table>
<thead>
<tr>
<th>Index</th>
<th>Donors, n =20</th>
<th>On admission</th>
<th>Control group</th>
<th>Test group I</th>
<th>Test group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOHb (418 nm), optical density unit/mg Hb</td>
<td>5.8±0.18</td>
<td></td>
<td>7.24±0.80 (+24.8%)</td>
<td>6.78±0.48 (+16.9%)</td>
<td>6.39±0.27 (+10.2%)</td>
</tr>
<tr>
<td>NOHb (545 nm), nmol/mg Hb</td>
<td>30.78±1.78</td>
<td></td>
<td>35.85±2.15 (+16.5%)</td>
<td>39.32±4.08 (+27.7%)</td>
<td>36.15±2.15 (+17.4%)</td>
</tr>
<tr>
<td>Conjugated dienes, nmol/mL</td>
<td>13.69±1.08</td>
<td></td>
<td>21.49±3.02 (+56.9%) P&lt;0.05</td>
<td>22.07±1.62 (+61.2%) P&lt;0.01</td>
<td>20.54±2.71 (+50.1%) P&lt;0.05</td>
</tr>
<tr>
<td>Malonic dialdehyde, nmol/mL</td>
<td>27.97±2.16</td>
<td></td>
<td>38.03±1.67 (+36.0%) P&lt;0.01</td>
<td>37.92±3.23 (+35.6%) P&lt;0.05</td>
<td>40.58±2.13 (+45.1%) P&lt;0.01</td>
</tr>
<tr>
<td>Schiff bases, arbitrary unit/mL</td>
<td>1.41±0.06</td>
<td></td>
<td>1.91±0.10 (+35.5%) P&lt;0.01</td>
<td>1.89±0.17 (+34.4%) P&lt;0.05</td>
<td>1.88±0.10 (+33.6%) P&lt;0.01</td>
</tr>
<tr>
<td>Catalase, nmol H₂O₂/ mL</td>
<td>16.31±1.24</td>
<td></td>
<td>12.01±2.02 (-26.3%) 0.05&lt;P&lt;0.01</td>
<td>12.04±2.13 (-26.2%) 0.05&lt;P&lt;0.01</td>
<td>12.79±1.35 (-21.6%) 0.05&lt;P&lt;0.01</td>
</tr>
<tr>
<td>Ceruloplasmin, µmol/L</td>
<td>1.31±0.08</td>
<td></td>
<td>0.62±0.10 (-52.9%) P&lt;0.01</td>
<td>0.92±0.17 (-29.5%) P&lt;0.05</td>
<td>0.72±0.09 (-45.0%) P&lt;0.01</td>
</tr>
</tbody>
</table>

Note: numbers in parentheses show the percentage of the index change as compared with donors; P - significance of change as compared with donors.

Nitrosohemoglobin is an intermediate complex of nitrogen oxide (NO), nitrogen fixation starts at any increase of its level in the body [8], as well as that in the early stage of local ischemia when NO increases the blood flow and decreases tissue damage [13]. However, rapid activation of nitrogen oxide synthesis in high-grade ischemia/hypoxia may become one of the causes of insult to cells during reoxygenation [13, 14].

Since the patients were admitted to the Acute Hemodialysis Department mainly on the 2nd -3rd day after the injury, we interpreted the rising tendency of the NOHb fractions as an indirect evidence of after sensation of hyperactive NO synthesis in response to acute tissue ischemia. This fact may be one of the triggers for the LPO activation in severe compression injury.

On admission all patients had a full-scaled picture of LPO activation consequences that showed as accumulated LPO products. So, the content of conjugated dienes in patient’s blood plasma exceeded the donor level in the control group by 56.9%, in the test group I –by 61.2%, and in the test group II – by 50.1%; MDA content – by 36.0%, 35.6%, and 45.1%, and Schiff base’s – by 35.5%, 34.4%, and 33.6% respectively.

Catalase activity had a downward tendency – it decreased by 26.3%, 26.2%, and 21.6% for the control group, test group I and II respectively, while ceruloplasmin
activity decreased significantly – by 52.9%, 29.5%, and 45.0% (P<0.05-0.01), which was indicative of lower reserves of plasma AOS.

All these data indicated that patients with ARF caused by a compression injury followed by arterial hypertension had free-radical activation of LPO processes in plasma that resulted in exhausted antioxidant protection of plasma by the 3rd-5th day of the post-injury period.

Blood plasma was tested biochemically by the time diuresis recovered and test results were compared between the groups. The results of the tests are given in Table 3.

It follows from the Table 3 that in the control group by diuresis recovery absolute indices of nitrosohemoglobin fractions level decreased to almost normal values, NOHb (418 nm) level exceeded the donor’s one by only 3.8%, and NOHb (545 nm) – by 11.0%. These data could be indicative of NO overuse as well as of lower levels of its synthesis or reduction. Such ‘normalization’ cannot be considered a good sign (that is why we put this term in quotes). It occurred when large masses of damaged soft tissues remained under hypoxia, when destructive processes were prevailing in renal tubules, anuria persisted, and patients had severe hypertension. Therefore we consider it as a failure of adaptation mechanisms aimed at improving of tissue perfusion in ischemic areas. This is proved by persistent significant activity of LPO and lower activity of enzymatic part of plasma AOS. The levels of conjugated dienes, MDA and Schiff bases remained higher than those of the donors by 46.5%, 39.3%, and 29.9% (P<0.01-0.05) and almost didn’t differ from the initial values. Catalase and ceruloplasmin activity remained low and differed from the donor’s levels by 20.9% (0.05<P<0.1) and 40.1% (P<0.01).

Table 3
The indices of LPO/AOS of blood plasma in all 3 groups on the 1st-2nd days of diuresis recovery

<table>
<thead>
<tr>
<th>Index</th>
<th>Donors, n =20</th>
<th>Diuresis recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control group</td>
<td>Test group I</td>
</tr>
<tr>
<td>NOHb (418 nm), optical density unit/mg Hb</td>
<td>5.8±0.18</td>
<td>6.02±0.38 (+3.8%) P&gt;0.1</td>
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<tr>
<td>NOHb (545 nm), nmol/mg Hb</td>
<td>30.78±1.78</td>
<td>34.15±2.96 (+11.0%) P&gt;0.1</td>
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<tr>
<td>Conjugated dienes, nmol/mL</td>
<td>13.69±1.08</td>
<td>20.05±2.37 (+46.5%) P&gt;0.05 P&lt;0.1</td>
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</tr>
<tr>
<td>Malonic dialdehyde, nmol/mL</td>
<td>27.97±2.16</td>
<td>38.97±2.00 (+39.3%) P&lt;0.01 P&lt;0.1</td>
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<td></td>
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<tr>
<td>Schiff bases, arbitrary unit/mL</td>
<td>1.41±0.06</td>
<td>1.83±0.09 (+29.9%) P&lt;0.01</td>
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</table>
Catalase, nmol H$_2$O$_2$/ mL | P$_1$>0.1 | P$_1$>0.1 | P$_1$<0.05 |
|------------------|--------|--------|--------|
| 16.31±1.24 | 12.90±1.35 (-20.9%) | 12.62±1.32 (-22.6%) | 16.05±1.25 *
| 0.05<P<0.1 P$_1$>0.1 | 0.05<P<0.1 P$_1$>0.1 | 0.05<P<0.1 P$_1$>0.1 | 0.05<P<0.1 P$_1$>0.1 |

Ceruloplasmin, µmol/L | 1.31±0.08 | 0.79±0.14 (-40.1%) | 1.12±0.07 * (-14.9%) | 1.08±0.09 * (-17.6%) |
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</thead>
<tbody>
<tr>
<td>0.05&lt;P&lt;0.1 P$_1$&gt;0.1</td>
<td>0.05&lt;P&lt;0.1 P$_1$&gt;0.1</td>
<td>0.05&lt;P&lt;0.1 P$_1$&gt;0.1</td>
<td>0.05&lt;P&lt;0.1 P$_1$&gt;0.1</td>
<td></td>
</tr>
</tbody>
</table>

Note: $P$ - significance of change as compared with donors; 
$P_1$ – significant of change as compared with initial values; 
numbers in parentheses show the percentage of the index change as compared with donors; 
* - 0.05<P<0.1 as compared with that in the control group; 
** - P<0.05 as compared with that in the control group; 
# - 0.05<P<0.1 as compared with that in the test group I; 
## - P<0.05 as compared with that in the test group I;

The test group I patients that were given Isradipine in multiple intensive therapy, had a different change in these indices. The levels of NOHb (418 nm) and NOHb (545 nm) were significantly higher that donor’s ones. So, as compared with the indices of the control group, the NOHb (418 nm) level in test group II patients significantly exceeded the donor’s one by 23.8%, and the NOHb (545 nm) level approximated to significantly higher values, exceeding the conventional norm by 37.3%. Increased NO level, which is indirectly proven by increased level of nitrosohemoglobin fractions, may be one of the components of the hypotensive effect of the medication, that some researchers describe [2].

As to the amount of LPO products, improved was noted only in the level of conjugated dienes that decreased from 61.2% to 27% and statistically approximated to the conventional norm, but the levels of MDA and Schiff bases remained higher by 39.8% and 27.9% than the conventional norm. Catalase activity (lower by 22.6% than the norm) was as low as on admission. However, ceruloplasmin activity increased slightly and then differed from the donor’s level only by 14.9% that made the activity statistically close to the donor’s level.

Although there were indirect signs of increased nitrogen oxide level that is a prooxidant, no signs of activated lipid peroxidation were identified in patients of the test group I. The activity of ceruloplasmin as one of the links of the anti-oxidant protection system, even tended to become normal. However, it should be noted that no significant improvement was found either in the described processes.

In the test group II whose patients were given SCENAR-therapy along with Isradipine, large increase in the level of nitrosohemoglobin fractions was evened off. NOHb (418 nm) level exceeded the donor’s one in this group by only 6.0%, and the level of NOHb (545 nm) – by 7.3% (P>0.1). These values turned out to be comparable with those in the control group. While in the control group we interpreted the low level of nitrosohemoglobin fractions as a negative event, in the test group II a comprehensive analysis of biochemical and clinical data showed their improvement. SCENAR-therapy decreased hyperactive synthesis of nitrogen oxide and/or its high release from vascular endothelium, which is indirectly indicated by normalized nitrosohemoglobin level, and also preserved and even intensified the direct action of
this calcium antagonist on smooth muscles of the vascular wall, as judged by blood pressure dynamics of the test group II patients. That could also be one of the reasons for practical reduction of oxidative stress in patients. The level of conjugated dienes and catalase activity in this group of patients became normal, and the levels of MDA, Schiff bases and ceruloplasmin activity also showed a tendency to become normal (0.05<P<0.1). However, in our opinion, the pronounced hypotensive and antioxidant effects that were observed in the test group II patients, could be directly associated with the regulating action of SCENAR on the patients’ bodies.

Findings

1. SCENAR-therapy in combination with Isradipine (2.5 mg twice daily) administered sublingually is the most effective method for adjusting blood pressure in patients with acute renal failure following the compression injury.
2. Isradipine causes increase in the level of nitrosohemoglobin fractions, especially NOHb (418 nm); notwithstanding the indirect signs of increased nitrogen oxide level that is a prooxidant, there was no activated lipid peroxidation. At the same time, no significant antioxidant improvement was found either.
3. Including SCENAR in the treatment provides evening-out of the effect of increasing level of nitrosohemoglobin fractions caused by Isradipine and practical reduction of the oxidative stress phenomena in blood plasma.

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