Фармакоэкономика
теория и практика

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№4 Том2 2014

- ФАРМАКОЭКОНОМИКА ТУБЕРКУЛЕЗА: МЕТОДОЛОГИЧЕСКИЕ ОСОБЕННОСТИ ПРОВЕДЕНИЯ ИССЛЕДОВАНИЙ
- ФИНАНСИРОВАНИЕ СИСТЕМЫ ЗДРАВООХРАНЕНИЯ НА РЕГИОНАЛЬНОМ УРОВНЕ. ВЗАИМОСВЯЗЬ КАЧЕСТВЕННЫХ И КОЛИЧЕСТВЕННЫХ ПОКАЗАТЕЛЕЙ С ВЕЛИЧИНОЙ ФИНАНСИРОВАНИЯ ЗДРАВООХРАНЕНИЯ

CLINICAL ECONOMIC EFFECTS OF REAMBERIN USE IN URGENT DISORDERS BASED ON RESULTS OF META-ANALYSIS

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Reamberin is a form of succinic acid for injections. Clinical economic effectiveness of reamberin was estimated for urgent diseases occurring while acute myocardial infarction, ischemic stroke and extensive liver resections. Reamberin addition to standard therapeutic schemes shortens hospital stay, diminishes complication rates, need for narcotic analgesics and use of expensive antibiotics combinations. Moreover, vegetative homeostasis was also normalized in reamberin using patients. Costs for gain of clinically valuable effect point were reduces down to 50% in reamberin subgroup.

Introduction

Hypoxia, energetic deficiency and vegetative homeostasis regulatory infringement accompany medical emergencies most frequently [3,4,7-10,13-15]. The damage of the other homeostasis systems develops in cascade manner, that leads to system defects and polyorgan insufficiency syndrome [4,13]. At acute period urgent vital functions correction in patients is possible with different drugs. Multiple drug prescription (polypragmasia) is usual while such medial conditions. It results at xenobiotic burden stressing biotransformation and substance removal, increase polyorgan insufficiency, starts additional central circulatory, microcirculatory damage and vegetative dysregulation.

Energy metabolism regulators are the powerful instrument to treat such pathological processes [5,7-9,11,16,17]. New pharmacological agents were developed specially for these disorders, in particular injection forms of adjuvant energy protectors (reamberin, cytoflavin, mexidol, remaxol). The remedies mentioned have systemic pharmacodynamics with signal (hormonal) [6] and substrate mechanisms of succinic acid, other mitochondrial agents and co-factors [11,16]. Due to mitochondrial functions' renovation at the loci of damage, succinic acid is a leader of energy supply for cellular adaptive reactions.

Clinical effectiveness of pharmacological protection while different disorders firmly, convincingly demonstrated in numerous researches previously. Administrative decisions to introduce succinic acid medicines into clinical practice must base on their clinical economic effectiveness study. So this article is devoted to valuation of reamberin clinical economic advantages while addition of the reamberin to basic treatment schemes during medical emergencies treatment. Hypoxia, energetic deficiency and vegetative dysregulation of different organs and systems are the steady followers of emergencies. It makes reasonable to estimate heterogeneity of numerous marker indicators responses.

Key words: *reamberin, acute myocardial infarction, extensive liver resections, ischemic stroke, urgent disorders, meta-analysis, cost-effectiveness analysis.*

Methods

The algorithms of evidence-based medicine and clinical effectiveness analysis were the basis of reamberin clinic- and pharmaco-economic evaluation. The controlled randomized prospective clinical trial with parallel groups design had strict inclusion criteria (previously reported [7-9]). The clinical patient documentation data were under comparison. The control groups received basic therapies (BT), the main group had treatment composed of mentioned basic schemes plus reamberin while acute period (BT + R). The reamberin administration included intravenous injections of 400 ml solution during 5-10 days in according with manufacturer's recommendations [11]. All together there were 232 cases of 3 nosologic emergency conditions proven as bound with hypoxic, energy deficit and vegetative homeostasis disregulative statuses [3,4,7,10,13-15]. These emergency conditions were: acute coronary syndrome without Q but linked with arterial hypertension (ACS+AH), ischemic stroke (IS), liver resections (LR). Certified medical specialists (therapists, cardiologists, neurologists, surgeons, emergency specialists) evaluated clinical status dynamics for all the participating patients and fixed data in clinical documents.

Patient data included the following informational clusters: 1). Symptoms, syndromes before and after the treatment according to clinical, laboratory, instrumental tests; 2). Drug administration (dosage for single intake and all the curse signature, the intake methods as pre os, intravenous etc.). The intake time was also under estimation, as well as the signs of coming effects/ ineffectiveness. Actual costs of medication included not only pharmacological agents, but also syringes, intravenous infusion systems etc.; 3). Marks about complications, adverse effects during the supervision period; 4). Complicated accounts of economic costs incl. medication (see p. 2), expenses of complicated medical services with hospital stay, diagnostic applications, additional complication treatment, medical specialists' fee. Web resource "Kirov pharmacy costs" allowed to appreciate the drugs' prices [19]. Economic departments of research-involved hospitals helped to assure precisely all the other expenses mentioned above.

Transitory (surrogate) pathology specific markers of effectiveness served as quantitative and qualitative frequency parameters of reamberin effects. Effectiveness calculation were rates of positive clinical outcomes (% of patients with main symptoms disappear, with somatic status improvement, % of complications' number decrease during fixed time cut) in BT and BT + R groups. Statistical tools with χ^2 criteria and $p<0,05$ were used.

The unified indicators of clinical efficiency were IAA (increase of absolute advantage), IRA (increase of relative advantage), NNT (number needed to treat - number of patients to treat traditionally during certain time for a favorable outcome comparable to a new way), OR (odds ratio - relation of improved outcome chances) and their 95% confidential intervals (95% of CI). The mathematic tool was meta-analysis calculator WinPepi published in the Internet network [1,12,20]. Sensitivity analysis [18] implied intra- and intergroup heterogeneity of indicative responses (χ^2, $p< 0,1$), «expense/ efficiency» (CER) coefficient's variability range dependent of minimal and maximal entire treatment drug dosage costs. As the work's aim was to integrate data of the same treatment efficiency (with/ without reamberin additionally) in patients with emergencies like myocardium damage, acute failure of cerebral blood supply or surgical aggression, also to form the conclusion about clinical and clinic-economic (pharmaco-economic) efficiency, the fixed effects' Mantel-Haenszel method [21] was applied within WinPepi program [20].

The results obtained were statistically processed step by step with STATISTICA 6,0 software [12]. There was analysis of distribution types with Kolmogorov-Smirnov/ Lilliefors and Shapiro-Wilk's criteria. The value distribution was not normal, so descriptive statistics was in format of Me [min;max] (M – median; min;max – minimal and maximal values). Non-parametric Mann-Whitney U-test was smart tool to evaluate statistical significance of quantitative intergroup difference.

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Clinic-economical effectiveness of reamberin was estimated with "Expenses-efficiency" method [2,18]. Expenses of hospital day stay and specific medications in resuscitation (other specialized) department (RD) compound patient direct costs. The "Expenses-efficiency" coefficients (CER, cost-effectiveness ratio) were calculated as ratio of drug expenses (CERmed) to clinical effectiveness index (% of patients with good outcome) for every marker parameter in comparison groups.

Results and discussion

Reamberin included in ACS+AH, IS, LR pharmacotherapy led to statistically significant difference between BR and BR+R patient groups for most in-hospital response parameters' end-points (Table 1). The united OR-matrix was created for all the indexes positive effects' figures due to reamberin use.

As the urgent cardiac damage happened (ACS+AH), statistically significant reamberin effects were anti-arrhythmic and anti-anginal. However, there was only tendency of systolic arterial pressure normalization same time.

There was reamberin use in liver resection also, and it resulted into statistically reliable acceleration of vegetative functions (peristaltic, independent patient seating and both early standing up and walking). Reamberin administration also led to inflammation decrease (less fever, pain, less terms of drainage with tubes) and more distinct immune activation (antibiotics cessation at 7-th day, less need to combine different antibiotics). At last, liver function improvement at 7-th day was also significant in reamberin group, as revealed ALT and AST parameters together with infusion therapy cessation rates. Interestingly, there was no between-group difference in surgical complications. Most probably, bigger number of patients would produce more informative results.

In case of reamberin use IS-patients demonstrated more transparent functional restoration of liver. It was explicit at the final patient inspection before hospital quit. Somehow neurologic symptoms showed only tendency to improve, that demand groups with more patients' numbers and longer in-clinic examinations for reliable comparison.

Thus the couple-group research of reamberin effectiveness in emergency conditions with resembled pathogenesis links (hypoxia, mitochondrial disregulation and failure of vegetative homeostasis) revealed the statistically significant difference between response parameters of comparison. The informative importance of these indexes was different, but absolute OR values steadily moved to reamberin use advantage (Fig. 1). Same time lowest 95% CI limits of several indexes crossed zero effect line (lgOR=1,0), that coincided with lack of statistic significance of χ^2 inter-group differences (Table 1). Within the comparison group variability of OR values depended on indicator response type, because different organism systems were unequally involved into poly-organic failure cascade, and their response to reamberin was different.

The heterogeneity bound OR in-group and inter-group unification increased stability of generalized efficiency assessment.

Table 1.
Influence of reamberin on frequency effectiveness characteristics, bound with basic therapy of emergency conditions and related hypoxia, vegetative disregulation

Emergency	Effectiveness criteria	χ^2	*p*	OR	[95% CI]
ACS+AH (n=106)*	1.Normal systolic arterial pressure at check out of hosp. (<140 mm hg)	2,902	0,088	2,20	[0,92;5,23]
	2.No arrhythmia complications	17,180	0,000	14,38	[3,23;64,05]
	3.No need to repeat narcotic adminictration	5,748	0,017	4,56	[1,24;16,76]
LR (n=50)*	1.Peristaltic restoration at 2nd day after surgery	5,094	0,024	4,89	[1,18;20,19]
	2. Independent seat in bed and walk at 3rd day after operation	4,023	0,045	3,27	[1,03;10,37]
	3.No fever at 5th day after surgery	5,556	0,018	4,33	[1,27;14,83]
	4.Drainage tubes pulled away at 4th day after operation	6,876	0,009	5,09	[1,48;17,47]
	5.Infusion therapy discontinued at 7th day after surgery	3,920	0,048	3,16	[1,02;9,80]
	6.Antibiotics discontinued at 7th day after operation	3,945	0,047	3,19	[1,02;9,94]
	7. No need to combine different antibiotics (2-3 drugs)	22,222	0,000…	51,00	[6,09;427,39]
	8. Cancellation of narcotic analgetics at 5th day after operation	3,125	0,077	2,92	[0,90;9,54]
	9.No complications after surgery	0,857	0,355	1,78	[0,53;5,94]
	10. Normal ALT/ AST ratio at 7th day after resection	9,441	0,002	16,00	[1,94;132,10]
IS (n=76)*	1.No residual movement disfunction at moment of discharge	1,852	0,174	2,43	[0,78;7,56]
	2.No speech disorders at moment of discharge	1,363	0,243	1,79	[0,72;4,45]
	3.No repeated in-hospital stroke	2,275	0,132	6,22	[0,75;51,68]
	4. Normal ALT/ AST ratio at moment of discharge	7,718	0,005	3,88	[1,50;10,06]

*Patients in ACS+AH cluster – 59 BT-group and 47 BT+R-group; patients in LR cluster – 25 patients in each group; patients in IS-cluster – 43 BT-group and 33 BT+R group. ALT – alanyn-amino-transferase, AST – aspartat-amino-transferase,

OR index in ACS+AH tests was 4,26 (95% CI 2,25 – 8,59), with Mantel-Haenszel amendment – 4,27 (2,28;8,00), heterogeneity χ^2 – 5,01, p=0,082. OR index in LR tests was 4,31 (95% CI 2,85 – 6,60), with Mantel-Haenszel amendment – 4,32 (2,29;6,45), heterogeneity χ^2 – 11,54, p=0,241. OR- index in IS tests was 2,73 (95% CI 1,54 – 4,93), with Mantel-Haenszel amendment – 2,77 (1,6;4,80), heterogeneity χ^2 – 1,95, p=0,582.

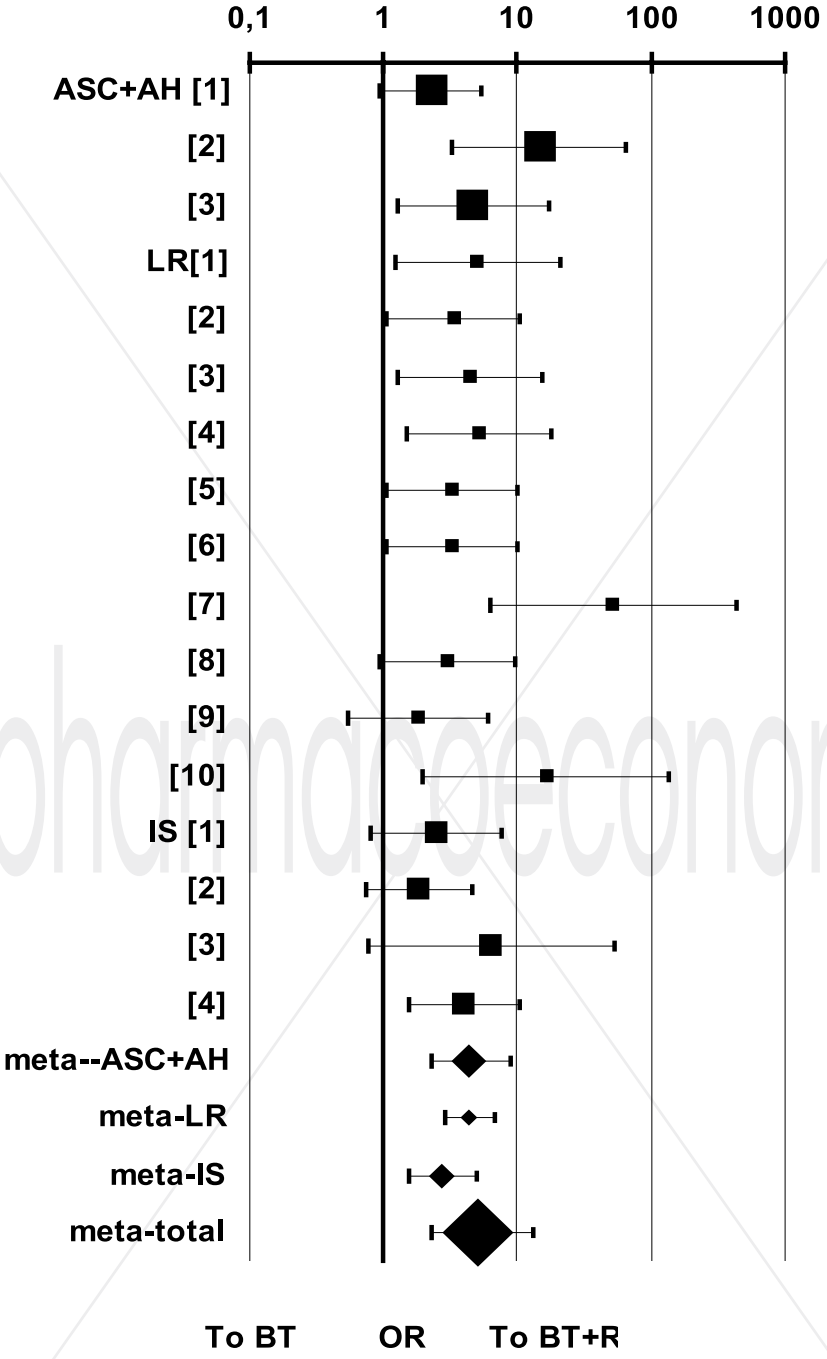


Fig. 1. OR variability range in case of reamberin use to treat emergencies with hypoxia and vegetative homeostasis disfunction (with 95% CI in logarithmic calculations: lgOR and 95% CI at "x" axis, vertical logarithm 1 axis is a line of zero effect; the points' square corresponds to numbers of cases investigated; «meta» – generalized meta-analysis results for in-group and between-group with different diseases).

To increase meta-analysis sensitivity all the 3 reamberin-in-emergencies' researches were united with singular positive outcome marker – "absence of complications during all the research time". For such design OR index was 5,14 (95% CI 2,25 – 13,01), with Mantel-Haenszel amendment – 5,25 (95% CI 2,33;11,81), heterogeneity χ^2 – 5,48, p=0,075. So the statistical significance of OR increased with results consolidation, 95% CI did not cross zero effect line and total formalized clinical effect clearly moved in advantage of reamberin (Fig.1).

Statistical power of efficiency heterogenic indexes was bound with parameters of clinical effectiveness increase (Table 2). Positive outcomes frequencies in main group (POR) stably exceeded the same parameters in control group (POC). IAA and IRA values reached or exceeded normal level [1,12] (IAA > 20%, IRA > 25%). The highest reamberin effect (IRA > 50%) was observed in LR group. Liver resections usually lead to massive bleedings, but reamberin acted as plasma substitute and hepatic protector.

Table 2
Reamberin influence on clinical effectiveness of treatment dedicated to hard conditions with hypoxia and vegetative disregulation

Pathology	Effectiveness criteria	POR, %	POC,%	IAA,%	IRA,%
ACS+AH (n=106)*	1.Normal systolic arterial pressure at check out of hosp. (<140 mm hg)	79	64	15	23
	2.No arrhythmia complications	96	51	45	88
	3.No need to repeat narcotic adminictration	93	77	16	21
LR (n=50)*	1.Peristaltic restoration at 2nd day after surgery	40	10	30	300
	2. Independent seat in bed and walk at 3rd day after operation	56	28	28	100
	3.No fever at 5th day after surgery	52	20	32	160
	4.Drainage tubes pulled away at 4th day after operation	56	20	36	180
	5.Infusion therapy discontinued at 7th day after surgery	64	36	28	78
	6.Antibiotics discontinued at 7th day after operation	60	32	28	88
	7. No need to combine different antibiotics (2-3 drugs)	68	4	64	1600
	8. Cancellation of narcotic analgetics at 5th day after operation	76	52	24	46
	9.No complications after surgery	76	64	12	19
	10. Normal ALT/ AST ratio at 7th day after resection	95	60	35	58
IS (n=76)*	1.No residual movement disfunction at moment of discharge	84	70	14	20
	2.No speech disorders at moment of discharge	50	39	11	28
	3.No repeated in-hospital stroke	100	84	16	19
	4. Normal ALT/ AST ratio at moment of discharge	71	39	32	82

*see Table 1 comments.

Reamberin administered additionally to ordinary pharmaco-therapy may be judged as effective medical technology, because NNT (table 3) figures occupied normalized [1,12] range 10 > NNT > 1. NNT reflects the quality of medical services.

Table 3
NNT range variability reflecting clinical effectiveness of treatment with reamberin administration

Pathology	Effectiveness criteria	NNT
ACS+AH (n=106)*	1.Нормализация САД (<140 мм рт.ст.)	5,3
	2.Отсутствие осложнений	6,3
	3.Отсутствие потребности в повторном введении наркотических анальге тиков	6,3
LR (n=50)*	1.Peristaltic restoration at 2nd day after surgery	3,3
	2. Independent seat in bed and walk at 3rd day after operation	3,6
	3.No fever at 5th day after surgery	3,1
	4.Drainage tubes pulled away at 4th day after operation	2,8
	5.Infusion therapy discontinued at 7th day after surgery	3,6
	6.Antibiotics discontinued at 7th day after operation	3,6
	7. No need to combine different antibiotics (2-3 drugs)	1,6
	8. Cancellation of narcotic analgetics at 5th day after operation	4,2
	9.No complications after surgery	8,3
	10. Normal ALT/ AST ratio at 7th day after resection	2,8
IS (n=76)*	1.No residual movement disfunction at moment of discharge	7,1
	2.No speech disorders at moment of discharge	9,1
	3.No repeated in-hospital stroke	6,3
	4. Normal ALT/ AST ratio at moment of discharge	3,1

*see Table 1 comments.

In BR group in-hospital stay duration of patients with ACS, LR and IS was 23-24 days in average, including resuscitation period (Table 4). The reamberin addition reduced this terms on 3-5 days. The treatment of patients in resuscitation department is much more complicated and expensive usually, than costs of usual in-hospital stay. So it affected the health care expenses drastically.
The drug expenses situated in the following sequence: ACS+AH< LR < IS (Table 5). Somehow the antibiotics of reserve or infusion treatment with albumin, frozen plasma, red blood cell's mass (LR), neuro-protectors (IS) made the costs' structure different for every disease [3,9,14]. Minimal and maximal figures of indexes, median figures differed unidirectional way in all the groups.

Table 4
Reamberin influence on the in-hospital stay while the emergency treatment

Pathology	Cost of one day in hospital, roubles (ResD/SurgD)	Treatment duration, days (ResD/SurgD)	
		BT	BT+R
ACS+AH	1358	24 [13;35]	20 [11;25]
LR	11252/1270	6 [2;8]/23 [17;30]	4 [2;6]/20 [11;20]
IS	14585/3780	6 [4;25]/23 [19;57]	5 [2;16]/18 [9;41]

ResD – resuscitation department; SurgD – surgical department. Terms description: [min;max] - mediana, minimal and maximal duration in all the sample.

The ACS+AH treatment was less expensive if reamberin was administered, the pure basic treatment cost more (nitrates, heparin, enalapril, Ca-channel blockers, diuretics etc. were spent in smaller quantities in BT+R group).

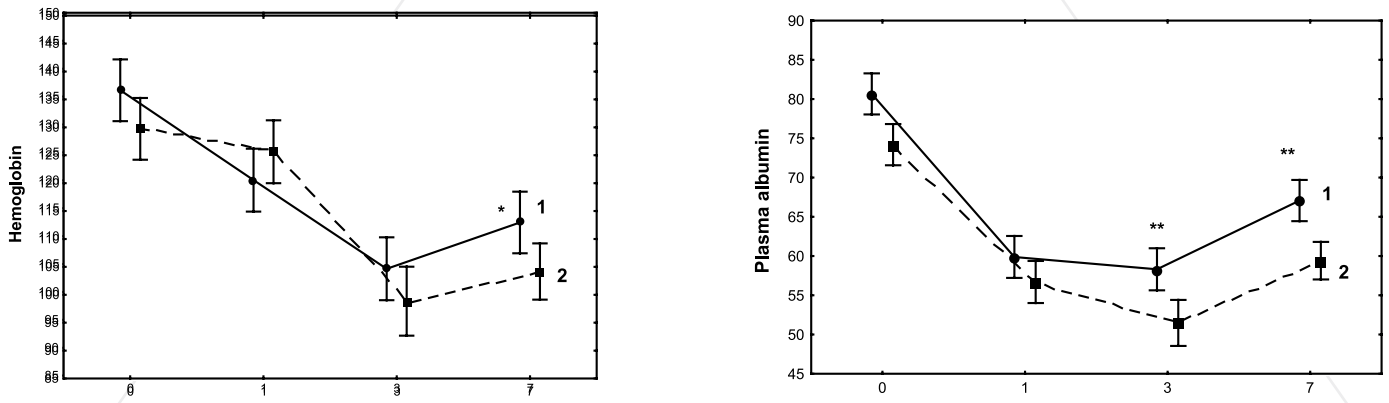
Table 5
The reamberin influence on the drug costs structure during ACS (without Q), IS, LR treatment

Indexes	Comparison groups		p
	BT	BT+R	
Cost of the basic medicines, entire treatment of 1 patient, rubles, Me,[min; max]			
ACS (without Q)			
Nitrates	72[43;291]	58[43;245]	NS
Heparin	195[88;362]	181[44;289]	0,034
ATF-inhibitors	74[32;170]	67[29;149]	NS
Others	211[106;478]	167[75;312]	0,047
Total	993[231;1495]	851[503;998]	0,042
LR			
Infusion/ transfusion remedies	6522[3998;9046]	3437[2605;4289]	0,010
Antibiotics	8413[3998;11578]	4435[2715;5365]	0,008
Others	9226[6128;13222]	7771[4703;7818]	0,011
Total	26658[11144;34927]	16731[7763;18457]	0,023
IS			
Antibiotics	682[167;4434]	662[152;1936]	NS
Hypotensive	184[107;767]	92[74;423]	0,005
Anticoagulants	403[51;809]	227[29;494]	0,001
Infusion/ transfusion remedies	1816[581;9154]	1488[434; 4768]	0,005
Neuro-protectors	1116[139;4951]	901[123;2805]	NS
Others	121[29;119]	55[17;534]	0,022
Total	3937[933;15844]	3143[552;9231]	0,041

Note. Entire treatment reamberin dose in BT+R group (400 ml per day intravenously) was 2200±560 ml (min 800 ml, max 4400 ml), Me – 1600 ml. Additional BT+R expenses to administer reamberin were 1047±209 rubles for all the treatment course (min — 374; max — 2560), Me 1432 rubles. Reamberin costs were included into total treatment costs. NS – not significant, p – level of statistical significance of inter-group difference, non-parametric Mann-Whitney U-test.

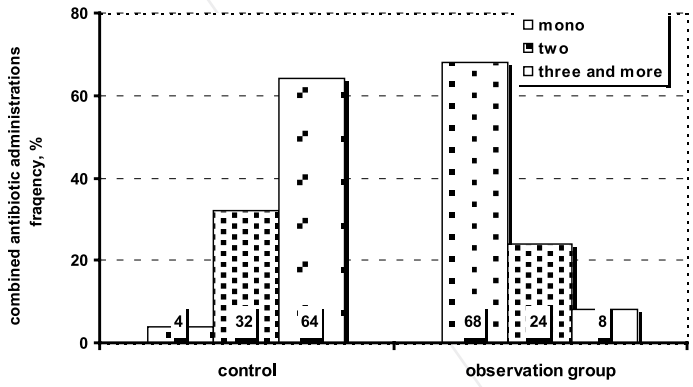
Use of reamberin reduced the need to provide infusions/ transfusions and antibiotics at least twice. Complete cancellation of infusion therapy on 7th day in BT+R group (see Table 2) took place in 64% of patients, in BT group – only in 36% treatment receivers (χ^2 = 65,4; p=0,047). Such reduction of infusion doses just led to double difference of infusion therapy expenses. The needs in albumines and red blood cells' mass, which are very expensive usually, also decreased, and also lowered total treatment costs. The after-operation loss of proteins in BT+R group was not massive, and hemoglobin scores were higher in BT+R group on 3rd and 7th days after resection (Fig.2).

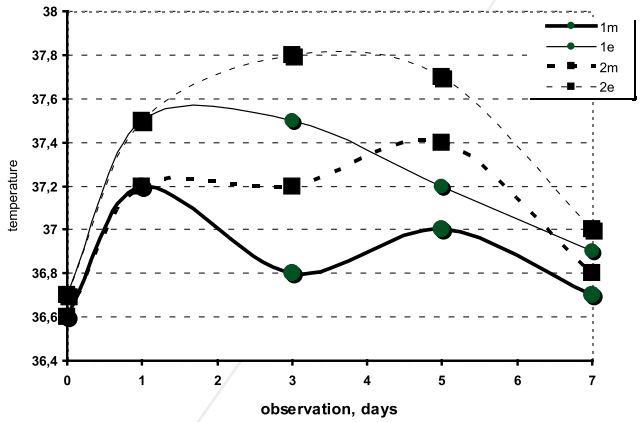
Fig.2. Blood analysis dynamics (left figure – hemoglobin, right – plasma albumin), both comparison groups in early postoperative period (LR). 1 – BT+R; 2 – BT-control. Intergroup difference is statistically significant (* - p<0,05; ** - p<0,01).



These factors influenced terms of drainage discontinuation (see Table 2). 4th day reamberin patients quitted drainage tubes unconvenience in 56% of cases (in control group – only 20%, χ^2 =74,36, p=0,0087).
At the 7th day after operations there was difference between groups in intensity of antibiotics use. BT+R group patients had less need in intensive antibiotics combination (Fig. 3). Absolute discontinuation of antibiotics use on 7th day after surgery took place in 60% cases of BT+R (only 32% in BT, (χ^2=65,5; p=0,047).

Fig.3. Reamberin and combined antibiotic administration, thermometry data («m» morning; «e» evening) in LR patients. 1, «observation group» – BT+R; 2, «control» – BT. «mono» 1 antibiotic, «two» 2 antibiotics, «three and more» 3 antibiotics and more. Left figure vertical axis – portion of patients, receiving antibiotics. Right figure vertical axis – body temperature; horizontal axis – observation, days.





So the reamberin led to more adequate antibiotic use. In BT+R group temperature became normal more rapid, so only one antibiotic was used in most cases. In control group numerous antibiotic administration was more frequent. The first range and reserve antibiotics did not differ in both groups, but total antibiotic cost was statistically different in BT+R and BT.
Reamberin use was a factor of structural treatment cost reduction in IS experiment. Maximal antibiotic expenses in BT+R and BT stroke patients' treatment did not differ. But antihypertensive, anticoagulant and infusion/ transfusion remedies' expenses reduced distinctly, significantly due to reamberin administration. Average neuro-protectors' cost was resembled in both groups, but there was tendency of expenses' decrease in most BT+R cases as it appeared in marginal [min; max] data. So the reamberin improved clinical effectiveness of IS treatment and shortened the terms of emergency period, in-hospital rehabilitation stay. Also reamberin decreased ksenobiotic liver load (see Table 2) and medication expenses considered in minimal/ maximal cost oscillations.
It is obvious, reamberin administration in all the experimental groups (ACS+AH, LR, IS) changed the economical profile of the treatment undertaken, changed same way despite the figural discrepancies and absolute value difference. Treatment terms and costs decreased, incl. resuscitation period. Total in-hospital stay and its' costs decreased. Total one-patient medication expenses reduced also (see Table 6).

Table 6
Reamberin influence on the costs' structure in comparison groups.

Pathology	Costs of one-patient treatment (Me [min;max])			
	Total one-day in-hospital stay, rubles		Total costs of entire treatment medications' dosage, rubles	
	BT	BT+R	BT	BT+R
ACS+AH	32592 [17654;47530]	27160 [14938;33950]	993 [231;1495]	851 [503;998]
LR	67512[22504;90016]/ 29210[21590;38100]	45008[22504;67512]/ 25400[13970;25400]	26658 [11144;34927]	16731 [7763;18457]
IS	87510[58340;364625]/ 86940[62340;215460]	72925[29170;233360]/68040[31170;154980]	3937 [933;15844]	3143 [552;9231]

Note: For LR and IS numerator – costs of resuscitation department; denominator – costs of surgical and neurology departments rehabilitation.

Reamberin included into traditional pharmacotherapy of emergencies improved clinical effectiveness of medical interventions via reduce of complications, of in-hospital stay duration, reduce of needs in medications and costs decrease.

Pharmaco-economical "costs-effectiveness" analysis revealed resource-saving properties of reamberin (see Table 7) for all the groups (ACS+AH, LR, IS). CER coefficient calculations obtained low (CER min) and high (CER max) drug cost limits. It was clear enough, that reaiberin reduced both limits distinctly in all the pathologies and despite of different response-indexes' frequency characteristics. Direction of the CER changes (ΔCER) was negative, and its' oscillations were negative also (ΔCERmin, % =-57 [-96; -17] and ΔCERmax, %= -62 [-97; -17]). Web data about drug prices in Kirov [19] brought information about 400 ml (1 bottle) reamberin price 187 – 256 rubles, approx. 36%. The variability vector (ΔCER) adopted this percentage, when sensitivity analysis "cost-effectiveness" was undertaken.

Table 7
Influence of reamberin on pharmaco-economical indexes of emergencies treatment effectiveness

Pathology	Effect marker*	CER **				ΔCERmin % ***	ΔCERmax % ***
		BTmin	BT+Rmin	BTmax	BT+Rmax		
ACS+AH	1	3,6	2,9	23,4	18,9	-19,0	-19,0
	2	4,5	2,4	29,3	15,6	-46,9	-46,9
	3	3,0	2,5	19,4	16,1	-17,2	-17,2
LR	1	1114,4	194,1	3492,7	461,4	-82,6	-86,8
	2	398,0	138,6	1247,4	329,6	-65,2	-73,6
	3	557,2	149,3	1746,4	354,9	-73,2	-79,7
	4	557,2	138,6	1746,4	329,6	-75,1	-81,1
	5	309,6	121,3	970,2	288,4	-60,8	-70,3
	6	348,3	129,4	1091,5	307,6	-62,8	-71,8
	7	2786,0	114,2	8731,8	271,4	-95,9	-96,9
	8	214,3	102,1	671,7	242,9	-52,3	-63,8
	9	174,1	102,1	545,7	242,9	-41,3	-55,5
	10	185,7	81,7	582,1	194,3	-56,0	-66,6
IS	1	13,3	6,6	226,9	109,9	-50,7	-51,6
	2	23,9	11,0	407,3	184,6	-53,9	-54,7
	3	11,1	5,5	189,1	92,3	-50,3	-51,2
	4	23,9	7,8	407,3	130,0	-67,5	-68,1

* figures meaning as in Table 1; ** CER in rubles/ % effect (outcomes frequencies in control and reamberin groups); *** ΔCER vector changings, markers of effect as in Table 1.

CER reduction in reamberin group against control group is a sign of clinical and pharmaco-economical effectiveness improvement [2,18]. Reamberin supported pharmacotherapy is adominant clinic-economical alternative to traditional schemes.

The leading cause of emergency conditions joint with ACS+AH, LR and IS are typical pathological processes in target-organs (heart, liver, brain) – hypoxia, energetic deficit, vegetative disregulation. Pharmacological correction of vital functions included administration of different groups' pharmacological agents (8-18 names) in accordance with standard protocols of patients' treatment.

Extracts form medical documentation revealed, that polypragmazia in ACS+AH group was 8 [5;10] drugs, in LR group was 14 [10;19] drugs, in IS group was 13 [8;19] drugs. Reamberin reduced analgetic demands in ACS+AH and LR groups, infusion/transfusion drugs' demands – in LR and IS groups, 2-4 antibiotics combinations' demands (in-hospital infections) – in LR and IS groups. It was important contribution of reamberin to pharmaco-economical effect component.

Conclusion

1). Unified parameters IAA, IRA, OR, NNT, CER allow to develop measuring scale and meta-analysis with clinical/ pharmaco-economical reamberin advantages approval. It is possible if reamberin is added to standard therapy of critical emergencies (ACS+AH, LR, IS) and amount of heterogenic response-indexes is documented.

2). Reamberin is adjuvant, energetic protector. It is produced with succinic acid. Reamberin has systemic pharmaco-dynamics, provides improvement of patients' status in cases of emergencies with different damage locations (myocardium, brain, liver).

3). Inclusion of reamberin into standard schemes of hard pathologic conditions' treatment with hypoxia, energetic deficiency, vegetative disregulation allows to increase clinical effectiveness of medical interventions. Reamberin reduces costs of clinical effect unit achievement more that for 50%, because in-hospital terms shorten, complications reduce and needs for expensive drugs become not so critical.

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