The Impact of Pre-emptive Large Dose of Methylprednisolone Combined With Gabapentin on Pain Treatment and Convalescence After Total Knee Arthroplasty in Elderly. A Randomized Control Study

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Research Article

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Abstract

Background The aim of the study was to assess whether administration of gabapentin and methylprednisolone as *"pre-emptive analgesia"* in a group of patients above 65 years of age would be effective in complex pain management therapy following total knee arthroplasty (TKA).

Material and Methods One hundred seventy, above 65 years old patients were qualified for the study, and 10 patients were excluded due to clinical situation. One hundred sixty patients were double-blind randomized into two groups: the study (eighty patients) and controls (eighty patients). The study group received as *"pre-emptive"* analgesia a single dose of 300 mg oral gabapentin and 125 mg intravenous methylprednisolone, while the others placebo. Perioperatively, all the patients received opioid and nonopioid analgesic agents calculated for 1 kg of body weight. We measured the levels of inflammatory markers (leukocytosis, C-reactive protein - CRP), pain intensity level at rest (numerical rating scale - NRS), the life parameters and all complications.

Results Following administration of gabapentin and methylprednisolone as *"pre-emptive"* analgesia CRP values being lower on all postoperative days (1, 2 days - p<0,00001, 3 day – p=000538), leukocytosis on day 2 (p<0,0086) and 3 (p<0,00042), the NRS score at rest 6, 12 (p<0,000001), 18 (p<0,00004) and 24 (p=0,005569) hours postoperatively . Methylprednisolone with gabapentin significantly decreased the dose of parenteral opioid preparations (p=0,000006). The duration time of analgesia was significantly longer in study group (p<0,000001). No infectious complications were observed; in the control group, one patient manifested transient ischaemic attack (TIA).

Conclusion The use of gabapentin and methylprednisolone at a single dose decreases the level of postoperative pain on the day of surgery, the dose of opioid analgesic preparations, the level of inflammatory parameters without infectious processes.

1. Introduction

Total knee arthroplasty (TKA) is performed in older patients due to degenerative lesions for improvement the quality of life. The postoperative period is associated with inconveniences, including pain of maximal intensity on day 1 [1]. Surgery, as a mechanical factor, initiates the pain process, incites nociceptors, evokes hyperalgesia, releases inflammatory mediators at the site of surgery and through damaging the vessels along with the anticoagulative and antiadhesive lining covering the vascular endothelial cells, initiates local as well as generalized the inflammatory process [2–4].

Prolonged administration of glucocorticoids in patients with osteoarthritis limits the inflammatory process, reduces chronic pain, through inhibition factors evoking hyperalgesia, synthesis of proinflammatory factors and blocking elements of the inborn immune system. The use of methylprednisolone at the dose of 125 mg as "*pre-emptive*" analgesia [5–9][10]has been also initiated since

2013, the Lundbeck Foundation of Denmark has been recommending using the medication as an element of the Enhanced Recovery After Surgery (ERAS) protocol in TKA [5–9,11].

Gabapentin is employed in managing chronic pain due to its effect exerted on cerebral modulation and perception of pain, somnolence as adverse effect, postoperatively, is beneficial [12,13].

1.1 Objective

The objective of the study was assessment of employing methylprednisolone and gabapentin in complex pain management in the perioperative period in patients above 65 years of age subjected to TKA. The authors attempted to answer whether administration of a single dose of methylprednisolone and gabapentin as *"pre-emptive"* analgesia would reduce: (1) the level of postoperative pain, the numerical rating scale (NRS) at rest every 6 hours on day 0, (2) the dose of parenteral analgesics agents, mainly opioids, (3) the occurrence of adverse effects that would delay early rehabilitation, (4) the inflammatory process parameters, (5) maintain stable glycemia levels.

2. Material And Methods

2.1 Study design and patients enrollment

This study was a single-center, prospective, double-blind randomized controlled trial conducted in a tertiary care hospital. Ethical approval for this study was provided by the Bioethics Committee of the Jagiellonian University, Krakow, Poland (nr 1072.6120.11.2020, 23/01/2020) and registered with ClinicalTrials.gov (ID: NCT04653415, 28/11/2020). All research was performed in accordance with relevant guidelines and the Declaration of Helsinki. After obtaining oral and written consent to participate in the study, consecutive patients above 65 years of age, operated on due to unilateral TKA in the period June 1 to December 31, 2019, with the procedures following the ERAS protocols were recruited. We excluded patients due to clinical situation that 1/ restricted glucocorticoid administration: diabetes type 1 and 2, CRP levels above normal values (≥ 5 mg/l), chronic steroid treatment, peptic ulcers treated in the past 30 days and 2/and the chronic pain in the course of gonarthrosis, high intensity requiring use opioids.

2.2 Randomization

Before surgery all the included patients were randomized into two groups - the study (pre-emptive large dose of methylprednisolone and gabapentin) and controls (placebo).The allocation was performed in the preanesthetic clinic. Individual not involved in the study prepared block randomization (block sizes 4 and 6) and used sealed envelope technique for allocation concealment. Clinical trial was coded by the topic manager without affecting the experimenters.

2.3 Procedure

First and foremost, prior to anesthesia induction, each patient received prophylactic anti-infection intravenous cephazolin 2.0 g, tranexamic acid 1.0 g for hemostasis control, and an anti-emetic agent – ondansetron 8 mg. Patients were then subjected to the standardized procedure of subarachnoid anesthesia with subsequent unilateral femoral nerve block on the operated side, followed by the surgical procedure – unilateral TKA. Fluid crystalloids administration was standardized to 12 ml/kg in the first hour of surgery, followed by 6 ml/kg for the remainder of surgery. Packed red blood cells were prepared in case if blood loss exceeded 600 ml and a hemoglobin concentration < 10 g/l during the time of operation. Pain management was carried out based on the results of the NRS scale at rest. Patient NRS scores were checked every 6 hours. Intravenous PCA (patient-controlled analgesia) with oxycodone hydrochloride was administered for NRS scores ≥ 4 points, and intravenous paracetamol with metamizole for NRS scores of 2–4 points. All pain medications were calculated for 1 kg of body weight. In keeping with the ERAS protocol, on the day of surgery, the patients received oral fluids and meals, were mobilized and rehabilitated.

The study Group M received as “pre-emptive” analgesia oral gabapentin − 300 mg, intravenous methylprednisolone − 125 mg, while the control Group K received an oral placebo – a tablet without any pharmacological properties, and 0.9% saline solution intravenously. The statistical analysis of the groups addressed the demographic dates, life parameters, general condition in keeping with the ASA (American Society of Anesthesiology), POSSUM (Physiologic and Operative Severity Score for the enUmeration of Mortality and Morbidity) score, total dose of analgesic medications administered parenterally calculated for 1 kg of body mass in response to value of NRS at rest on day 0, time of administration of the first dose, and duration of peripheral nerve block. On the day of surgery and on subsequent days, indicators were made based on glycaemia levels and inflammatory markers: C-reactive protein (CRP) and leukocytosis (WBC) levels.

2.4 Statistical analysis

The statistical analysis was performed using the T-Student test for independent groups employing the Cochran-Cox modification; the resultant statistical significance was $p < 0.05$ (PQStat v 1.6.8 software). A statistical power analysis was also conducted to validate the adequacy of the sample size (> 80%).

3. Results

The analysis included a group of elective 170 patients above 65 years of age, operated on due to unilateral TKA in the period June 1 to December 31, 2019, with the procedures following the ERAS protocols in our department. From the study were excluded 10 patients due to clinical situation that 1/ restricted glucocorticoid administration: diabetes type 1 and 2, CRP levels above normal values (≥ 5 mg/l), chronic steroid treatment, peptic ulcers treated in the past 30 days and 2/and the chronic pain in the course of gonarthrosis, high intensity requiring use opioids.The schematic flowchart as per the CONSORT is given in Fig. 1.

The two groups of patients were numerically comparable: Group M consisted of 80, Group K of 80 patients. No differences were seen between the groups in mean age, duration of surgery, initial and postoperative life parameters (excluding the pulse rate on day 0 in the control group), perioperative risk according to the ASA scale, postoperative efficiency, possible complication development, perioperative mortality to the POSSUM scale, comorbidities. Significantly longer time of postoperative hospitalization values were seen in the controls group (Table 1, 2).

Table 1
General data describing the analyzed elderly patients (over 65 years old) divided into the study group (M) and the controls (K).

Data	Group (M)	Group (K)	p- value
n	80	80	
Age (years)	73.5 ± 7.47	71.36 ± 5.23	0.21
Mean hospitalization time (days)	3.98 ± 0.92	5.81 ± 1.45	0.010
Mean postoperative hospitalization time (days)	3.01 ± 0.96	4.87 ± 1.15	0.0113
Postoperative MAP ^ (mmHg)	96.39 ± 8.23	98.87 ± 10.99	0.328
Postoperative pulse (x/min)	68.75 ± 15.08	77.78 ± 21.50	0.0093
Postoperative Sp02 (%)	98.17 ± 0.98	98.60 ± 0.70	0.053
^ Mean Arterial Pressure			

Table 2
Distribution of comorbidities and anesthesia in the analyzed patients aged above 65 years old divided into the study group (M) and the controls (K).

Data	Group M		Group K		p-value
	n	%	n	%	
n	80	100.00	80	100.00	
Hypertension arterial	80	100.00	80	100.00	
Atrial fibrillation, arrhytmia supraventricular	9	11.25	9	11.25	
IHD, myocardial infarction in anamnesis	8	10	9	11.25	0.564
COPD grade III	6	7.5	5	6.25	0.789
TIA in anamnesis	6	7.5	5	6.25	0.621
Cerebral tumor in anamnesis	1	1.25	2	2.5	0.356
Regional anesthesia	80	100.00	80	100.00	
Femoral nerve block- analgesia	80	100.00	80	100.00	
ASA^ II	66	82.5	60	75	0.326
ASA^ III	14	17.5	20	25	0.129
POSSUM* physiological (points)	17.42 ± 3.28		18.06 ± 4.45		0.537
POSSUM* morbidity (%)	26.22 ± 12.91		26.54 ± 15.13		0.029
POSSUM* mortality (%)	4.38 ± 3.55		4.94 ± 3.16		0.513
IHD: ischaemic heart disease					
COPD: chronic obstructive pulmonary disease					
TIA: transient ischaemic attack					
^ American Society of Anesthesiology Score,					
* Physiological and Operative Severity Score for the enumeration of Morbidity and Mortality					

In the postoperative period the analysis focused on inflammatory parameters in the two groups: leukocytosis levels, CRP values on day 0, 1, 2, 3 postoperatively in blood and in surgical wound drainage on day 0, glycemia levels in consecutive postoperative days, pain sensation on day 0 based on the NRS scale at rest every 6 hours, dosage of analgesic agents administered on the day of surgery (Table 3, Fig. 2, Fig. 3),

Table 3
Leukocytosis levels in the analyzed patients aged above 65 years old divided into the study (M) and control (K) groups.

Data	Group (M)	Group (K)	OR	-95 CI	p-value
n	80	80			
Initial blood leukocytosis level (x10^3/μL)	6.82 ± 1.38	6.91 ± 1.88	− 0.083	− 0.94 / 0.77	0.846
Initial blood leukocytosis level – day 0 (x10^3/μL)	11.63 ± 2.52	10.92 ± 2.50	0.714	− 0.57 / 2.00	0.272
Blood leukocytosis level – day 1 (x10^3/μL)	13.78 ± 3.53	11.83 ± 3.35	1.94	0.17 / 3.71	0.031
Blood leukocytosis level – day 2 (x10^3/μL)	10.08 ± 2.48	11.96 ± 2.85	− 1.88	− 3.26 /- 0.49	0.0086
Blood leukocytosis level – day 3 (x10^3/μL)	8.24 ± 1.85	10.96 ± 2.93	− 2.71	− 4.16 /- 1.27	0.00042
Initial blood CRP* level (mg/l)	3.09 ± 3.33	2.69 ± 1.55	0.39	− 0.90 / 1.69	0.543
Blood CRP* level – day 0 (mg/l)	8.91 ± 12.07	18.33 ± 12.69	− 9.42	− 15.8 /- 3.03	0.0045
Blood CRP* level – day 1 (mg/l)	28.39 ± 21.57	61.06 ± 24.57	− 32.66	− 44.61 / − 20.71	< 0.000001
Blood CRP* level – day 2 (mg/l)	53.92 ± 41.89	105.52 ± 32.68	− 51.60	− 70.71 /- 32.48	< 0.000001
Blood CRP* level – day 3 (mg/l)	53.85 ± 51.04	97.12 ± 36.12	− 43.27	− 66.83 /- 19.72	0.000538
Wound drainage fluid CRP* level (mg/l)	8.09 ± 10.61	5.29 ± 4.37	2.79	− 1.24 / 6.84	0.171
Initial blood glucose level (mmol/l)	6.13 ± 1.13	5.79 ± 1.10	0.33	− 0.23 / 0.91	0.247
Blood glucose level – day 0 (mmol/l)	7.63 ± 0.90	7.66 ± 1.05	− 0.02	− 0.53 / 0.48	0.910
Blood glucose level – day 1 (mmol/l)	7.70 ± 0.83	7.94 ± 0.90	− 0.23	− 0.68 / 0.21	0.295

*CRP – C reactive protein

OR – odds ratio

CI – confidence interval

Data	Group (M)	Group (K)	OR	-95 CI	p-value
Blood glucose level – day 2 (mmol/l)	6.82 ± 0.62	7.14 ± 0.69	– 0.31	– 0.66 / 0.02	0.068
Blood glucose level – day 3 (mmol/l)	5.79 ± 0.58	5.88 ± 0.53	– 0.09	– 0.38 / 0.19	0.505
*CRP – C reactive protein					
OR – odds ratio					
CI – confidence interval					

The time of femoral nerve block, identical to the time of administration of the first analgesic medication dose, was significantly longer in the study group.

Only 21 of 80 subjects (26%) received oxycodone hydrochloride in view ≥ 4 points NRS score at rest in the study group, whilst 71 of 80 patients (89%) in the controls group.

4. Discussion

The large joint arthroplasty, in agreement ERAS protocol requires analgesic management for initiation of rehabilitation as early as on the day of surgery [14,15]. This proceeding limits the time of hospitalization, the risk of infectious and other complications [1,2,14–16].

The mean postoperative hospitalization in the present material did not differ from data currently reported in publications and meta-analyses[7,11,14,16–19] equaling 3.01 days in the study group. In the control group this time was significantly longer - by two days (p = 0.0113); due to:

- prolonged, more severe pain on day 0, is illustrated by the level of pain at the NRS scale, this necessitated employing higher doses of analgesics, including opioids (Fig. 2, Fig. 3),

- difficulties in achieving flexion movement of the knee subjected to the surgical procedure; what was noted in two patients, whose hospitalization were prolonged until 8 and 9 days,

- development of a significant complication in an 82-year old male: transient ischaemic attack (TIA), on day 2 postoperatively, the patient was discharged without any focal signs on day 20 postoperatively.

The ERAS protocol reduced the postoperative time of hospitalization following TKA the average until 3 days, similarly as in our material. The observation is illustrated by the meta-analysis addressing the years 1990–2015 presented by [17]. Similarly, in Gotland's hospitals in the period of 2011–2015 the postoperative hospitalization time of 6374 patients following TKA was shortened from 5 days to 3 days (patients classified ASA I and II score, irrespectively of age) [18]. *Vehmeijer B et al (2018)* presented the evaluation of the so-called "outpatient" hospitalization after TKA based on data from Danish centers in

the years 2014–2017, only 15 to 20% of patients were discharged earlier than after 23 hours of postoperative hospitalization, the remaining individuals required hospitalization longer than one day [19,20].

The analysis of 1246 patients by *Osinski et al (2019)* evaluated the effect of the type of anesthesia with analgesic peripheral block employed in the course of unilateral TKA, the mean postoperative hospitalization time was shorter by 0,9 day in patients who received regional anesthesia as compared to general anesthesia, up to day 4 postoperatively achieved better flexion movement in the implanted knee joint, by the mean value of 10 [17,21]. In our material, all patients received regional anesthesia with analgesic peripheral block, we observed 2 patients in the study and control groups with difficulties in achieving satisfactory flexion of the operated joint. In study group that time for two patients were shorter than almost double than it was in control group - by 5 days v.s. 8 and 9 days, the difference in time resulted from one variable: administration of methylprednisolone and gabapentine in “pre-emptive” analgesia.

The authors analyzed patients above 65 years of age. In some populations this is still the age that opens the ”older patients” group. More frequently the literature on the subject defines the elderly group as including patients above 85 years of age since this is the age at which a progressive decrease of the functional reserve occurs, leading to increased morbidity and mortality. At present it is difficult, to follow the standpoint of biologists, related to progress in life and in medical sciences, to include patients whose age starts at 65 or even 75 years of life in the group of the ”elderly” patients [22]. Our material showed no intergroup differences in initial state, severity of comorbidities with respect to their state as measured by the ASA and POSSUM scales (Table 2). A complication – TIA, occurred in the controls in a patient in whom no abnormalities, including blood flow to central nervous system (CNS) (echocardiography, electrocardiography, cervical and spinal vessels). Searching for various causes of the complication development since it occurred in the control group which received no methylprednisolone, an agent that stabilizes circulatory parameters in the postoperative period, stabilizes the vascular endothelial lining that shows antiadhesive and anticoagulatory parameters in the postoperative period [4,9]. With exception of the above, the present authors did not observe any systemic complications or deaths. The staff of the Orthopedic Center, University Hospital of Copenhagen did not observe significant difference of circulatory system parameters on the day of surgery in the course of mobilization, rehabilitation in patients after TKA into two groups, one with *”pre-emptive”* analgesia with methylprednisolone and the controls where no methylprednisolone was administered [23]. ”Methylprednisolone” patients did not demonstrate any signs of subjective intolerance of verticalization as opposed to the control group where 40% of the individuals interrupted verticalization [23].

In the group of the patients analyzed in the present material, methylprednisolone with gabapentin as “*pre-emptive”* analgesia significantly decreased the employed dose of all parenteral analgesics - opioids – oxycodone hydrochloride, paracetamol, metamizol in mg/kg body weight per day. The time of the first opioid dose administration after surgery completion measured in hours was also different in the two groups (Fig. 3). It was the consequence of pain experienced at rest as measured by the NRS scale at

every 6 hours postoperatively (Fig. 2); this is the explanation of the significantly higher pulse in the postoperative period in the controls as compared to the study group (Table 1). Starting in 2007, publications have been presenting the effect of preoperative administration of first dexamethasone, subsequently methylprednisolone[15, 22–25] on the postoperative period: postoperative hospitalization time, infectious complications, stability of the circulatory system following the initial mobilization, pain at rest and during activity [6,7,14,16,18–20,23,25–30].

Gabapentin as the analgesic medication due to its inhibitory effect exerted on the nociceptors is employed alone or in combination with celecoxib as "*pre-emptive"* analgesia [16]. A significant decrease of the dose of analgesic preparations, including opioid agents, as employed in pain management on the day of TKA followed by their use in consecutive three days 1 hour before mobilization allowed for effective rehabilitation and achieving proper degree of knee joint flexion what was presented by [8].

The literature on the subject evaluated parameters as CRP level, but also endogenous anti-inflammatory protein pentraxin-3, markers of vascular endothelial dysfunction that initiate inflammatory processes: syndecan-1, thrombomodulin, sE-Selectin, or vascular endothelial growth factor (VEGF) [4,8,9,26–29]. In 2017, *Lindberg-Larsen* with coworkers demonstrated significantly higher levels of pentraxin-3 in the groups of patients who were administered a single dose of methylprednisolone, in the first 24 hours postoperatively and documented the absence of topical and generalized inflammatory processes [24]. Numerous authors demonstrated the CRP level lacking significance when the two groups were compared [26]. In the present material, the analysis included the following inflammatory parameters: leukocytosis was significantly higher on day 1 in the study group as opposed to the controls, yet on subsequent days (day 2 and 3 postoperatively), it was significantly lower in the study subjects (Table 3). In turn, CRP values were significantly lower in all time sequences in the group of methylprednisolone-administered patients as compared to the controls. Drainage fluid CRP levels did not differ in the two groups. The two groups were initially statistically comparable with respect to leukocytosis and blood CRP values (Table 3).

As it was demonstrated in the present material, a single dose of methylprednisolone did not significantly affect fluctuations of glycemia levels in the analyzed patients, it should be emphasized, that patients with glucose intolerance were excluded from the study (Table 3). Similar observations are reflected in data reported in the literature on the subject: among others, by [22].

Degenerative lesions involving the peripheral neurons occurring in the process of aging lead to prolonged conduction within all peripheral nerves, the excitability threshold of sensory receptors is elevated – this is true for pain receptors too [22]. The peripheral block time as the time of subarachnoid anesthesia are prolonged. In the presented material, the time of subarachnoid neuraxial anesthesia with supplementary peripheral blockade of the femoral nerve was significantly different in the two groups, being almost threefold longer in the study group as compared to the controls. As the material encompassed patients above 65 years of age whose reactions to topical anesthesia medications were similar, the difference in time resulted from one variable: administration of methylprednisolone in "*pre-emptive"* analgesia (Fig. 3).

5. Conclusion

In summary, the use of a single dose of gabapentin and methylprednisolone as *"pre-emptive analgesia"* in the group of patients above 65 years old: (1) measurably decreases postoperative pain levels assessed in keeping with the NRS scale at rest in all time intervals on the day of surgery unilateral TKA and decreases the dose of analgesic agents, including opioid preparations (oxycodone hydrochloride), (2) significantly lower levels of inflammatory parameters: CRP values have been demonstrated on all postoperative days, leukocytosis levels on day 2 and 3 postoperatively, (3) supports circulatory system stability, (4) no statistical difference has been demonstrated in glycemia levels, (5) no occurrence of adverse effects that would delay early rehabilitation of the patient in accordance with the ERAS protocol.

Declarations

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Competing interests

The authors declare no competing interests.

Data statement

Data will be made available on request.

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Figures

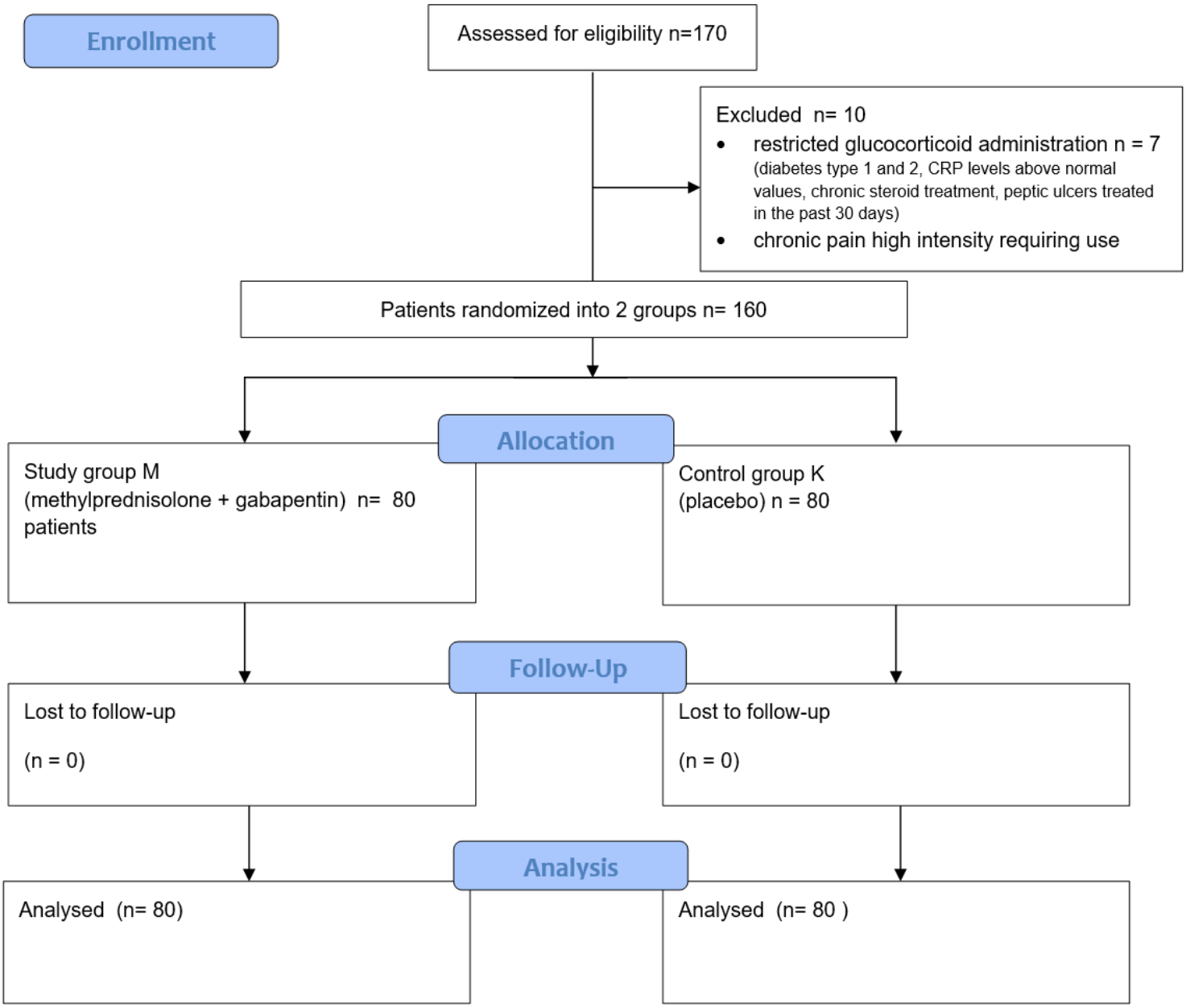

Figure 1

A schematic diagram showing the CONSORT flowchart.

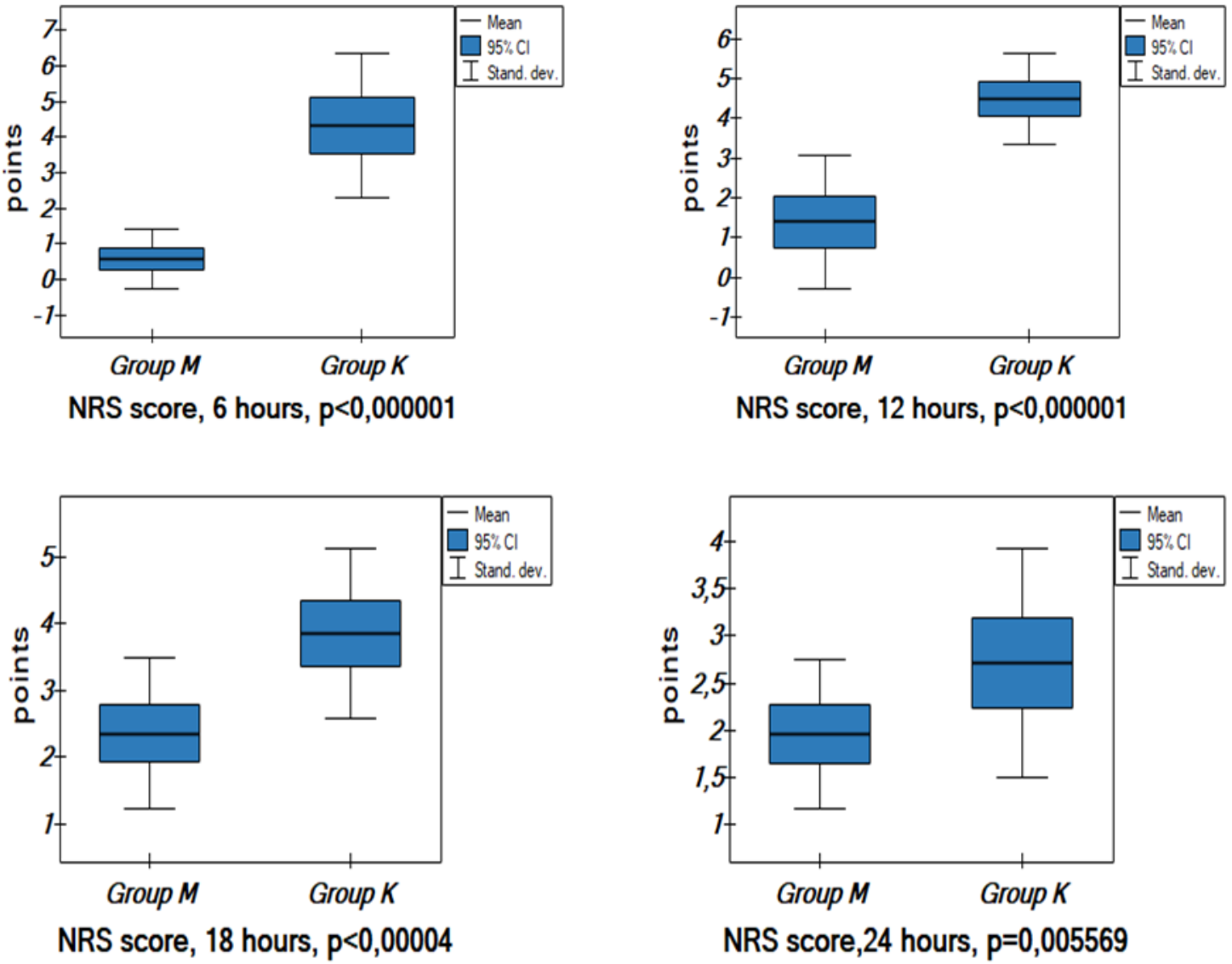

Figure 2

NRS level (points) at rest at time points at 6, 12, 18 and 24 hours postoperatively in the analyzed patients above 65 years of age divided into the study (M) and control (K) groups.

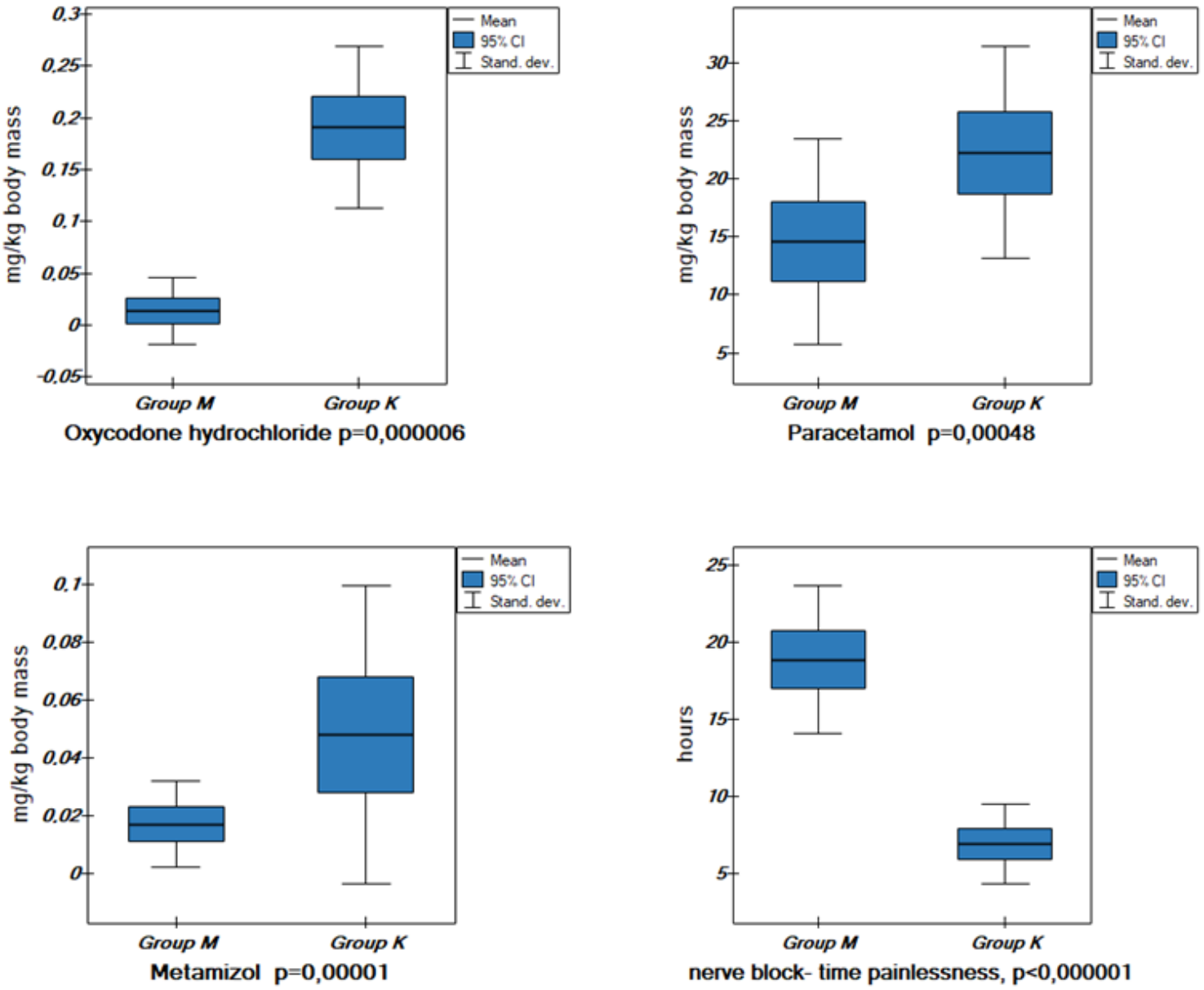

Figure 3

Dose of oxycodone hydrochloride in mg/kg body weight, paracetamol in mg/kg body weight, metamizole in g/kg body weight and time of postoperative analgesia in hours (h) not requiring administration of an analgesic agent in the analyzed patients above 65 years old divided into the study (M) and control (K) groups on day 0.