**Objective:** To evaluate the therapeutic value of melatonin, mesenchymal stem cells and their extracellular vesicles, exosomes, on renal ischemia–reperfusion.

**Methods:** Female albino rats (n = 64) were divided into eight groups (n = 8 per group):

control, sham (only laparotomy), renal ischemia–reperfusion (renal ischemia–reperfusion +phosphate-buffered saline), melatonin (renal ischemia–reperfusion + melatonin), mesenchy-mal stem cells (renal ischemia–reperfusion + mesenchymal stem cells), exosomes (renalischemia–reperfusion + exosomes), melatonin + mesenchymal stem cells (renal ischemia–reperfusion + melatonin + mesenchymal stem cells) and melatonin + exosomes (renal ischemia–reperfusion + melatonin + exosomes). After the establishment of the renal ischemia–reperfusion model, rats in each group were bilaterally injected once with either mesenchymal stem cells or exosomes in both renal arteries during reperfusion.

**Results:** Notable improvement of renal ischemia–reperfusion was obtained after different treatments, as evidenced by a lower histopathological score of kidney injury; decreased serum levels of urea, creatinine and retinol-binding protein; reduced lipid peroxidation marker malondialdehyde; increased superoxide dismutase and catalase activities; reduced apoptosis (lower DNA damage and B-cell lymphoma 2-associated X protein, and higher B-cell lymphoma 2 genes/proteins); and inhibition of kidney inﬂammatory and damage markers (tumor necrosis alpha, interleukin-1b, nuclear factor kappa B, kidney injury molecule-1, IL-18, matrix metalloproteinase 9, neutrophil gelatinase-associated lipocalin). The improvement order was (highest to lowest): melatonin + exosomes, melatonin + mesenchymal stem cells, exosomes, mesenchymal stem cells and melatonin group.

**Conclusions:** Our data suggest a potential therapeutic effect of combined therapy with melatonin, mesenchymal stem cells and their exosomes to minimize renal ischemia– reperfusion injury in rats.